**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re: U.S. Patent No. 6,992,110

Inventors: Kranzler *et al.*

Assignee: Cypress Bioscience, Inc.

Title: METHODS OF TREATING FIBROMYALGIA SYNDROME, CHRONIC FATIGUE SYNDROME AND PAIN

Issue Date: January 31, 2006



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**REQUEST FOR EXTENSION OF PATENT TERM**
**UNDER 35 U.S.C. § 156**

Mail Stop: **Hatch-Waxman PTE**
Office of Patent Legal Administration
Room MDW 7D55
600 Dulany Street (Madison Building)
Alexandria, VA 22314

Sir:

Cypress Bioscience, Inc. ("Cypress") hereby requests an extension of the term of U.S. Patent No. 6,992,110 ("the '110 patent") pursuant to 35 U.S.C. § 156. A copy of the '110 patent is attached as Exhibit A. The assignment of the '110 patent from the inventors to Cypress has been recorded at reel 012773, frame 0222 on March 27, 2002. A copy of the recorded assignment is attached as Exhibit B.

A total of five copies of this Request are submitted in compliance with 37 C.F.R. § 1.740(b) and as suggested by MPEP § 2753.



As permitted by 37 C.F.R. § 1.785(b) and MPEP § 2761, Cypress is concurrently filing a request for patent term extension of U.S. Patent No. 6,602,911 based upon the same regulatory review period.

The following information is submitted in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740, and follows the numerical format set forth in 37 C.F.R. § 1.740(a):

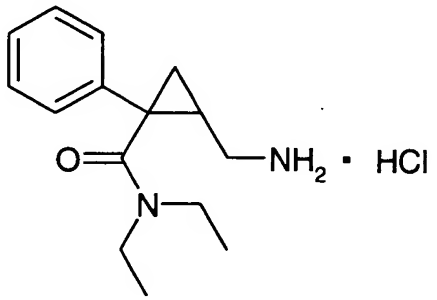
**(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics.**

The approved product will be marketed under the trademark SAVELLA™ in 12.5 mg, 25 mg, 50 mg, and 100 mg tablets for the management of fibromyalgia. A copy of the approved package insert for SAVELLA™ is attached as Exhibit D. The active ingredient of SAVELLA™ has

(a) the chemical name cis-(±)-2-(aminomethyl)-N,N-diethyl-1-phenyl-yclopropanecarboxamide hydrochloride;

(b) the generic name milnacipran hydrochloride;

(c) the structural formula:




(d) the empirical formula C15H23ClN2O; and

(e) a molecular weight of 282.8 g/mol.

**(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred.**

The regulatory review occurred under Section 505(b) of the Federal Food, Drug and Cosmetic Act (FFDCA), which is codified at 21 U.S.C. § 355(b). Section 505(b) (21 U.S.C. § 355(b)) provides for the submission and approval of New Drug Applications (NDAs).

**(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred.**

Milnacipran hydrochloride received permission for commercial marketing from the Food and Drug Administration (FDA) pursuant to Section 505(b) of the FFDCA (21 U.S.C. § 355(b)) on January 14, 2009. A copy of the letter from the FDA approving marketing of milnacipran hydrochloride is attached as Exhibit E.

**(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.**

The active ingredient in the approved product is milnacipran hydrochloride. Milnacipran hydrochloride was not previously approved for commercial marketing or use under the FFDCA, the Public Health Service Act, or the Virus-Serum-Toxin Act prior to the approval on January 14, 2009.

**(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the date of the last day on which the application could be submitted.**

Milnacipran hydrochloride was approved for commercial marketing on January 14, 2009. The sixty day period expires on Saturday, March 14, 2009, assuming January 14 is the first day of the sixty day period. The present application, therefore, is timely filed within the sixty day period.

**(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration.**

Inventors: Jay D. KRANZLER

Srinivas G. RAO

Patent No.: 6,992,110

Issue Date: January 31, 2006

Expiration Date: November 5, 2021

**(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings.**

A copy of the '110 patent is attached as Exhibit A.

**(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent.**

A copy of two terminal disclaimers filed on June 16, 2005 are attached as Exhibit J.

A copy of a certificate of correction filed on March 30, 2006 is attached as Exhibit K.

The 3½ year maintenance fee for the '110 patent is not due until approximately July 31, 2009.

**(9) A statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on:**

- **(i) The approved product, if the listed claims include any claim to the approved product;**
- **(ii) The method of using the approved product, if the listed claims include any claim to the method of using the approved product; and**
- **(iii) The method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product.**

The '110 patent claims methods of using the approved product, milnacipran hydrochloride, to treat pain in an animal subject. Each applicable patent claim is set forth below together with a showing of the manner in which each applicable patent claim reads on the approved product.

> 1. A method of treating pain in an animal subject, comprising administering to an animal subject suffering from pain, an effective amount of milnacipran, or a pharmaceutically acceptable salt thereof, alone or in combination with a compound that is not phenylalanine, tyrosine or tryptophan.

The approved product is indicated for the management of fibromyalgia which is characterized by widespread pain. *See* Exhibit D (Approved Package Insert).

> 4. The method according to claim 1, wherein the animal subject is human.

The approved product is indicated for the management of fibromyalgia in humans. Fibromyalgia is characterized by widespread pain. *See* Exhibit D (Approved Package Insert).

> 5. The method according to claim 1, wherein the amount administered is from about 25 mg to about 400 mg per day.

The approved product has been approved for daily dosages up to 200 mg/day, *e.g.*, 25 mg/day, 50 mg/day, 100 mg/day, and 200 mg/day. *See* Exhibit D (Approved Package Insert).

**(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:**

**(i) For a patent claiming a human drug, antibiotic, or human biological product:**

**(A) The effective date of the investigational new drug (IND) application and the IND number;**

**(B) The date on which a new drug application (NDA) application or a Product License Application (PLA) was initially submitted and the NDA or PLA number; and**

**(C) The date on which the NDA was approved or the Product License issued;**

The investigational new drug (IND) application for milnacipran was assigned Application No. 63,736. Cypress Bioscience, Inc. filed the IND application on November 30, 2001 (Exhibit F). The IND became effective on January 2, 2002; thirty days after the FDA received the IND request from Cypress. *See* 21 U.S.C. § 355(i)(2).

The NDA for milnacipran hydrochloride, NDA 22-256, was submitted to the FDA on December 18, 2007 (Exhibit H).

NDA 22-256 was approved by the FDA on January 14, 2009 (Exhibit E).

**(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.**

Cypress Bioscience, Inc. submitted an IND application for milnacipran on November 30, 2001 (Exhibit F). The IND (No. 63,736) became effective on January 2, 2002 (Exhibit G).

The initiation of a Phase II trial of milnacipran hydrochloride in the treatment of fibromyalgia by Cypress was publicly announced on February 25, 2002. Enrollment of this study was completed on September 10, 2002, and preliminary results were announced on December 10, 2002, with formal top-line results being announced on February 10. The results of this study were supportive of further development, and the first Phase III study was initiated on October 21, 2003.

Cypress entered into a License and Collaboration Agreement with Forest Laboratories, Inc. ("Forest") on January 9, 2004, to jointly investigate and develop milnacipran as a therapeutic. On October 1, 2004, Forest was designated as the regulatory agent for Cypress. Cypress and Forest began a joint investigation of milnacipran. The studies referenced in the IND were begun and the FDA was notified of Protocol Amendments and amendments to the Chemistry, Manufacturing and Control Sections and Pharmacology Sections of the IND. Cypress and Forest also submitted the required information about investigators, and the required 15-day alert reports.

On December 18, 2007, Forest submitted an NDA for milnacipran hydrochloride, which was assigned number 22-256 (Exhibit H). The NDA was approved on January 14, 2009 (Exhibit E). Exhibit I provides the chronology of regulatory review of milnacipran hydrochloride.

**(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of the extension was determined.**

It is the opinion of the Applicant that the '110 patent is eligible for patent term extension under 35 U.S.C. § 156(a). The Applicant claims an extension of 435 days.

**Statement of Eligibility of the Patent for Extension**

**Under 35 U.S.C. § 156(a)**

Section 156(a) provides in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted; (2) the term of the patent has never been extended under 35 U.S.C. § 156(e)(1); (3) the application for extension is submitted by the owner of record of the patent or its agent and in accordance with 35 U.S.C. § 156(d)(1)-(4); (4) the product has been subject to a regulatory review period before its commercial marketing or use; and (5) except for 35 U.S.C. §§ 156(a)(5)(B) and 156(a)(5)(C), the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.

Each of these elements is satisfied here:

(1) The term of the '110 patent expires on November 5, 2021. This application has, therefore, been submitted before the expiration of the patent term.

(2) The term of the '110 patentf has never been extended under 35 U.S.C. § 156(e)(1).

(3) The application is submitted by Anthony C. Tridico, an attorney for the law firm Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, which has been appointed

under a limited power of attorney to act for the owner of the '911 patent for the purpose of filing this Request (Exhibit C). This application is submitted in accordance with 35 U.S.C. § 156(d) within the sixty-day period beginning January 14, 2009, when the product received permission for marketing under the FFDCA and contains the information required under 35 U.S.C. §§ 156(d)(1)(A)-(E).

(4) The product was the subject of IND 63,736 (filed on November 30, 2001; effective on January 2, 2002), and NDA 22-256 (filed on December 18, 2007 and approved on January 14, 2009). Thus, the product was subject to a regulatory review period under § 505(b) of the FFDCA before its commercial marketing or use.

(5) Finally, the permission for the commercial marketing of the approved product after regulatory review under FFDCA § 505(b) is the first permitted commercial marketing of the approved product in the United States. This is confirmed by the absence of any approved NDA under which the approved product could be commercially marketed prior to January 14, 2009.

**Statement as to the Length of the Extension Claimed**

**In Accordance with 37 C.F.R. 1.775**

The term of the '110 patent should be extended by 435 days. The extension was determined according to 37 C.F.R. § 1.775 and the PTO worksheet "Calculation of Length for Patent Term Extension for a Human Drug Product" as follows:

| | | |
|---|---|---|
| (1) | 2176 | The number of days in the period beginning on the effective date of the IND (January 2, 2002) and ending on the date the NDA was initially submitted (December 18, 2007). This is the "testing phase" as defined in 37 C.F.R. § 1.775(c)(1). |
| (2) | 393 | The number of days in the period beginning on the date the NDA was initially submitted (December 18, 2007) and ending on the date of NDA approval (January 14, 2009). This is the "approval phase" as defined in 37 C.F.R. § 1.775(c)(2). |
| (3) | 2569 | The sum of (1) and (2). This is the regulatory review period as define in 37 C.F.R. § 1.775(c). |
| (4) | 0 | The number of days in the approval phase (2) which were on and before issuance of the '110 patent. 37 |

| | | |
|---|---|---|
| | | C.F.R. § 1.775(d)(1)(i). |
| (5) | 0 | The number of days in the approval phase (2) during which the Applicant did not act with due diligence. 37 C.F.R. § 1.775(d)(1)(ii). |
| (6) | 0 | The sum of (4) and (5). |
| (7) | 2569 | The difference between the regulatory review period (3) and (6). 37 C.F.R. § 1.775(d)(1)(ii). |
| (8) | 1490 | The number of days of the period of the testing phase (1) which occurred prior to the issuance of the '110 patent. 37 C.F.R. § 1.775(d)(1)(i). |
| (9) | 0 | The number of days of the period of the testing phase (1) during which the Applicant failed to act with due diligence 37 C.F.R. § 1.775(d)(1)(ii). |
| (10) | 1490 | The sum of (8) and (9). |
| (11) | 1079 | The difference between the regulatory review period (7) and (10). |
| (12) | 2176 | The number of days of the testing phase (1). |
| (13) | 1490 | The number of days from (10). |
| (14) | 686 | Subtract line (13) from line (12) |
| (15) | 343 | One half of (14) 37 C.F.R. § 1.775(d)(1)(iii)[1] |
| (16) | 736 | Subtract line (15) from line (11) |
| (17) | November 5, 2021 | The original expiration date of the '110 patent. |
| (18) | November 11, 2023 | The expiration date of the '110 patent if the original expiration date is extended by the number of days in line (16). 37 C.F.R. § 1.775(d)(2) |
| (19) | January 14, 2009 | The date of approval of the application under § 505(b) of the FFDCA. |
| (20) | 14 years | The limitation of 37 C.F.R. § 1.775(d)(3). |
| (21) | January 14, 2023 | The number of years in (20) plus the date on (19). 37 C.F.R. § 1.775(d)(3). |
| (22) | January 14, 2023 | The earlier of line (18) or line (21) |
| (23) | November 5, 2021 | The original expiration date of the '110 patent. |
| (24) | 5 years | The applicable limitation of 37 C.F.R. § 1.775(d)(5) |
| (25) | November 5, 2026 | The number of years on (24) plus the date on (23). |

[1] 37 C.F.R. § 1.775(d)(1) provides that for purposes of subtraction, half days are ignored.

| | | |
|---|---|---|
| (26) | January 14, 2023 | The earlier of line (22) or line (25) |
| (27) | November 5, 2021 | The original expiration date of the '110 patent |
| (28) | 435 | The number of days which is the difference between the date on line (27) and the date on line (26) |

**(13) A statement that the Applicant acknowledges a duty to disclose to the Commission of Patents and Trademarks and to the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.**

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and to the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought for the '110 patent by this Request as required by 37 C.F.R. § 1.765.

**(14) Prescribed Fee:**

Please charge the required fee of $1,120.00 as required under 37 C.F.R. § 1.20(j)(1) to Deposit Account No. 06-0916. The Commissioner is authorized to charge any additional fees to Deposit Account No. 06-0916.

**(15) The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed**

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& Dunner, LLP
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In view of the foregoing, Cypress Bioscience, Inc., requests that the Commissioner grant an extension of 435 days to U.S. Patent No. 6,992,110.

Favorable action is earnestly solicited.

Respectfully submitted,

Dated: 3/10/09

Anthony C. Tridico

# List of Exhibits

Exhibit A - U.S. Patent No. 6,992,110

Exhibit B - Assignment of the '110 patent from the inventors to Cypress

Exhibit C - Limited Power of Attorney Authorizing Anthony C. Tridico to Act on Behalf of Cypress

Exhibit D - Approved package insert for SAVELLA™

Exhibit E - FDA Approval Letter

Exhibit F - Letter dated November 30, 2001 submitting IND 63,736

Exhibit G - Letter from FDA acknowledging November 30, 2001 submission of IND 63,736

Exhibit H - Letter dated December 18, 2007 submitting NDA 22-256 to FDA

Exhibit I - Chronology of Regulatory Review of SAVELLA™

Exhibit J - Terminal disclaimers filed on June 16, 2005

Exhibit K - Certificate of correction filed on March 30, 2006

# EXHIBIT A

US006992110B2

(12) **United States Patent**
**Kranzler et al.**

(10) **Patent No.: US 6,992,110 B2**
(45) **Date of Patent: Jan. 31, 2006**

(54) **METHODS OF TREATING FIBROMYALGIA SYNDROME, CHRONIC FATIGUE SYNDROME AND PAIN**

(75) Inventors: **Jay D. Kranzler**, La Jolla, CA (US); **Srinivas G. Rao**, San Diego, CA (US)

(73) Assignee: **Cypress Bioscience, Inc.**, San Diego, CA (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 12 days.

(21) Appl. No.: **10/623,378**

(22) Filed: **Jul. 18, 2003**

(65) **Prior Publication Data**

US 2004/0229956 A1 Nov. 18, 2004

**Related U.S. Application Data**

(60) Division of application No. 10/028,547, filed on Dec. 19, 2001, now Pat. No. 6,602,911, which is a continuation-in-part of application No. 10/014,149, filed on Nov. 5, 2001, now Pat. No. 6,635,675.

(51) **Int. Cl.**
*A61K 31/165* (2006.01)

(52) **U.S. Cl.** ..... **514/620**

(58) **Field of Classification Search** ..... 514/620
See application file for complete search history.

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*Primary Examiner*—Rebecca Cook
(74) *Attorney, Agent, or Firm*—Darby & Darby

(57) **ABSTRACT**

The present invention provides a method of treating fibromyalgia syndrome (FMS), chronic fatigue syndrome (CFS), and pain in an animal subject. The method generally involves administering a therapeutically effective amount of a dual serotonin norepinephrine reuptake inhibitor compound or a pharmaceutically acceptable salt thereof, wherein said dual serotonin norepinephrine reuptake inhibitor compound is characterized by a non-tricyclic structure and an equal or greater inhibition of norepinephrine reuptake than serotonin reuptake. In particular, the use of milnacipran to treat FMS, CFS, and pain is disclosed.

**6 Claims, No Drawings**

# METHODS OF TREATING FIBROMYALGIA SYNDROME, CHRONIC FATIGUE SYNDROME AND PAIN

This application is a divisional of U.S. Ser. No. 10/028,547 filed Dec. 19, 2001, now U.S. Pat. No. 6,602,911, entitled "Methods of Treating Fibromyalgia Syndrome, Chronic Fatigue Syndrome and Pain" by Jay D. Kranzler and Srinivas G. Rao, which is a continuation-in-part of U.S. Ser. No. 10/014,149 filed Nov. 5, 2001, now U.S. Pat. No. 6,635,675.

## 1. FIELD OF THE INVENTION

The present invention relates to methods for the treatment of fibromyalgia syndrome, chronic fatigue syndrome, and pain. In particular, the present invention relates to methods of treating fibromyalgia syndrome, chronic fatigue syndrome, and pain with a sub-class of dual serotonin norepinephrine reuptake inhibitors characterized by a non-tricyclic structure and inhibit the reuptake of norepinephrine to an equal or greater extent than they inhibit the reuptake of serotonin.

## 2. BACKGROUND OF THE INVENTION

Fibromyalgia syndrome (FMS) is the most frequent cause of chronic, widespread pain, estimated to affect 2–4% of the population. FMS is characterized by a generalized heightened perception of sensory stimuli. Patients with FMS display abnormalities in pain perception in the form of both allodynia (pain with innocuous stimulation) and hyperalgesia (increased sensitivity to painful stimuli). The syndrome, as defined by the American College of Rheumatology's criteria, involves the presence of pain for over 3 months duration in all four quadrants of the body, as well as along the spine. In addition, pain is elicited at 11 out of 18 "tender points" upon palpation. Other associated symptoms include fatigue, nonrestorative sleep, and memory difficulties.

Chronic fatigue syndrome (CFS) is a debilitating disorder characterized by profound tiredness or fatigue. Patients with CFS may become exhausted with only light physical exertion, and must often function at a level of activity substantially lower than their capacity before the onset of illness. In addition to the key defining characteristic of fatigue, CFS patients generally report various nonspecific symptoms, including weakness, muscle aches and pains, excessive sleep, malaise, fever, sore throat, tender lymph nodes, impaired memory and/or mental concentration, insomnia, and depression. Like patients with FMS, patients with CFS suffer from disordered sleep, localized tenderness, and complaints of diffuse pain and fatigue.

There are two widely used criteria for diagnosing CFS. The criteria established by the U.S. Centers for Disease Control and Prevention include medically unexplained fatigue of at least six months duration that is of new onset, not a result of ongoing exertion and not substantially alleviated by rest, and a substantial reduction in previous levels of activity. In addition, the diagnosis involves the determination of the presence of four or more of the following symptoms—subjective memory impairment, tender lymph nodes, muscle pain, joint pain, headache, unrefreshing sleep, and postexertional malaise (>24 hours). Reid et al., 2000, *British Medical Journal* 320: 292–296. The diagnostic criteria from Oxford includes severe, disabling fatigue of at least six months duration that affects both physical and mental functioning and the fatigue being present for more than 50% of the time. In addition, the diagnosis involves the determination of the presence of other symptoms, particularly myalgia and sleep and mood disturbance. Reid et al., 2000, *British Medical Journal* 320: 292–296.



Owing to their common symptomology, FMS and CFS are thought to be related. However, they manifest different major symptoms. Whereas pain is the major symptom reported by patients with FMS, fatigue is the major symptom reported by patients with CFS. Given their relatedness, these two indications have been treated with the same medications. Some of the common medications currently employed to treat CFS and/or FMS include, but are not limited to, analgesics, hypnotics, immune suppressants, various other prescribed medications, and an array of non-prescription medications. Although a broad array of medications are used in FMS and CFS patients, no single pharmacological agent or combination of agents is effective in the treatment of either of these disorders. Thus, due to the lack of effective treatment regimens for FMS and/or CFS, there is a need to develop effective treatments.

Pain is associated with a variety of different underlying illnesses or injuries. Pain may be either acute or chronic. Chronic or intractable pain is often endured over many years or decades. Patients suffering from chronic pain often develop emotional problems which can lead to depression and in the worst case, attempted suicide. Long lasting pain often occurs particularly in joints, in muscles, connective tissue and in the back. In the United States alone, chronic pain causes a loss of more than 250 million working days per year. A patient is considered to have chronic pain when complaints thereof last longer than six months. In the course of time, chronic pain may form an independent clinical syndrome.

Most analgesic agents in use today are not always effective, may produce serious side effects and can be addictive. Hence, there is a demand for more active analgesic agents with diminished side effects and toxicity, and which are non-addictive. The ideal analgesic would reduce the awareness of pain, produce analgesia over a wide range of pain types, act satisfactorily whether given orally or parenterally, produce minimal or no side effects, and be free from the tendency to produce tolerance and drug dependence.

## 3. SUMMARY OF THE INVENTION

In one aspect, the invention provides a method of treating fibromyalgia syndrome (FMS) and/or the symptoms associated therewith in an animal subject, including a human. The method generally involves administering to an animal subject suffering from FMS an effective amount of a dual serotonin norepinephrine reuptake inhibitor ("SNRI") compound of a specific type, or a pharmaceutically acceptable salt thereof. The SNRI compounds that are useful to treat FMS and/or symptoms associated therewith are characterized by a non-tricyclic structure and inhibit the reuptake of norepinephrine to an equal or greater extent than they inhibit the reuptake of serotonin (referred to hereinafter as "NE≧5-HT SNRI compounds"). In one embodiment of the invention, the NE≧5-HT SNRI compound administered inhibits norepinephrine reuptake to a greater degree than it inhibits serotonin reuptake (referred to hereinafter as a "NE>5-HT SNRI compound"). One particular example of such a NE>5-HT SNRI compound is milnacipran, or a pharmaceutically acceptable salt thereof. In another embodiment, the NE≧5-HT SNRI compound is not administered adjunctively with phenylalanine, tyrosine and/or tryptophan.

In another aspect, the invention provides a method of treating pain in an animal subject, including a human. The method generally involves administering to an animal subject suffering from pain an effective amount of a NE≧5-HT SNRI compound, or a pharmaceutically acceptable salt thereof. In one embodiment, a NE>5-HT SNRI compound is administered. One particular example of a NE>5-HT SNRI compound is milnacipran or a pharmaceutically acceptable salt thereof. In another embodiment, the NE≧5-HT SNRI compound is not administered adjunctively with phenylalanine, tyrosine and/or tryptophan.

In still another aspect, the invention provides a method of treating CFS and/or symptoms associated therewith. The method generally involves administering to a patient suffering from CFS an effective amount of a NE≧5-HT SNRI compound, or a pharmaceutically acceptable salt thereof. In one embodiment, a NE>5-HT SNRI compound is administered. One particular example of a NE>5-HT SNRI compound is milnacipran or a pharmaceutically acceptable salt thereof. In another embodiment, the NE≧5-HT SNRI compound is not administered adjunctively with phenylalanine, tyrosine and/or tryptophan.

In yet another aspect, the invention provides a kit comprising a NE≧5-HT SNRI compound packaged in association with instructions teaching a method of using the compound according to one or more of the above-described methods. The kit can contain the NE≧5-HT SNRI compound packaged in unit dosage form. In one embodiment, a NE>5-HT compound can be included in the kit. One particular example of a NE>5-HT SNRI compound is milnacipran or a pharmaceutically acceptable salt thereof.

## 4. DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

### 4.1 Abbreviations

CFS chronic fatigue syndrome
FMS fibromyalgia syndrome
5-HT serotonin
NARIs norepinephrine specific reuptake inhibitors
NE norepinephrine
NMDA N-methyl D-aspartate
NSAIDs non-steroidal anti-inflammatory drugs
SSRIs selective serotonin reuptake inhibitors
TCAs tricyclic antidepressants
SNRIs dual serotonin norepinephrine reuptake inhibitors

### 4.2 Definitions

The term "dual serotonin norepinephrine reuptake inhibitor compound" or SNRI refers to the well-recognized class of anti-depressant compounds that selectively inhibit reuptake of both serotonin and norepinephrine. Common SNRI compounds include, but are not limited to, venlafaxine, duloxetine, and milnacipran.

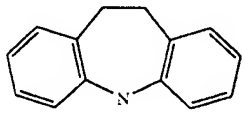
The terms "NE≧5-HT SNRI" and "NE>5-HT SNRI" refer to particular subclasses of SNRI compounds that are useful in the methods and kits of the present invention, as will be described in more detail herein.

### 4.3 Treatment of FMS, CFS and/or Pain

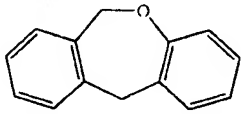
The present invention provides methods and kits for treating FMS, CFS, and pain. A particular subclass of SNRI compounds is useful for practicing the present invention. Compounds in this SNRI subclass, referred to as "NE≧5-HT SNRI compounds," inhibit norepinephrine reuptake more than or equal to serotonin reuptake. Moreover, the NE≧5-HT compounds of the invention exclude compounds that belong to the distinct class of antidepressant compounds commonly referred to in the art as tricyclic antidepressants or TCAs. In particular, compounds useful for practicing the present invention inhibit norepinephrine reuptake more than serotonin reuptake, referred to as "NE>5-HT SNRI compounds."

Tricyclic antidepressants (TCAs) are a well-recognized class of antidepressant compounds that are characterized by a dibenz[b,e]azepine (structure I), dibenz[b,e]oxepine (structure II), dibenz[a,d]cycloheptane (structure III) or dibenz[a,d]cycloheptene (structure IV) tricyclic ring structure. These various rings are depicted below:

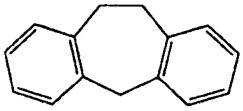
(I)



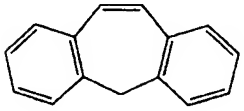
(II)



(III)

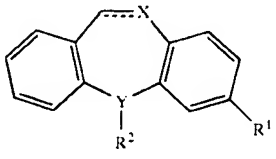


(IV)



The TCAs are typically substituted at position 1 of the tricyclic ring with alkylamines or alkylidenamines, and may include additional substituents (typically on the benzo groups). Many common TCAs, including imipramine, desipramine, clomipramine, trimipramine, amitriptyline, nortriptyline, doxepin, cyclobenzaprine and protriptline are characterized by the general formula (V), below:

(V)



wherein:
X is O or C;
Y is N or C;
$R^1$ is H or Cl;
$R^2$ is selected from the group consisting of $—(CH_2)_3N(CH_3)_2$, $—(CH_2)_3NHCH_3$, $—CH_2CH(CH_3)CH_2N(CH_3)_2$, $=CH(CH_2)N(CH_3)_2$, $=CH(CH_2)_2NHCH_3$ and $—(CH_2)_3NHCH_3$; and
the dotted line represents a single bond or a double bond.

The NE≧5-HT SNRI compounds of the invention exclude compounds classified as tricyclic antidepressants, and thus exclude compounds characterized by the above-depicted fused tricyclic nuclei of structures (I), (II), (III), and (IV).

As mentioned above, the NE≧5-HT SNRI compounds useful in the methods and kits of the invention include

compounds that inhibit norepinephrine reuptake to a greater extent than serotonin reuptake, as well as compounds that inhibit the reuptake of these two monoamines to an equivalent extent. In one embodiment of the invention, the NE≧5-HT SNRI compounds have a ratio of inhibition of norepinephrine reuptake to serotonin reuptake ("NE:5-HT") in the range of about 1–100:1. In a particular embodiment, the compounds are NE>5-HT SNRI compounds, i.e., compounds that inhibit norepinephrine reuptake to a greater extent than serotonin reuptake. Such NE>5-HT SNRI compounds generally have a NE:5-HT in the range of about 1.1–100:1. That is, such NE>5-HT SNRI compounds are at least 1.1 to about 100 times more effective at inhibiting norepinephrine reuptake than serotonin reuptake. NE>5-HT SNRI compounds having a NE:5-HT ratio in the range of about 2:1 to about 10:1 may be particularly effective.

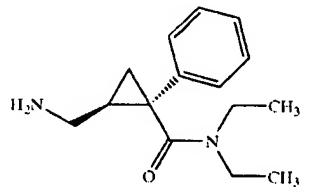
Various techniques are known in the art to determine the NE:5-HT of a particular SNRI. In one embodiment, the ratio can be calculated from $IC_{50}$ data for NE and 5-HT reuptake inhibition. For example, it has been reported that for milnacipran the $IC_{50}$ of norepinephrine reuptake is 100 nM, whereas the $IC_{50}$ serotonin reuptake inhibition is 200 nM. See Moret et al., 1985, *Neuropharmacology* 24(12):1211–1219; Palmier et al., 1989, *Eur J Clin Pharmacol* 37:235–238. Therefore, the NE:5-HT reuptake inhibition ratio for milnacipran based on this data is 2:1. Of course, other IC values such as $IC_{25}$, $IC_{75}$, etc. could be used, so long as the same IC value is being compared for both norepinephrine and serotonin. The concentrations necessary to achieve the desired degree of inhibition (i.e., IC value) can be calculated using known techniques either in vivo or in vitro. See Sanchez et al., 1999, *Cellular and Molecular Neurobiology* 19(4):467–489; Turcotte et al., 2001, *Neuropsychopharmacology* 24(5):511–521; Moret et al. 1985, *Nueropharmacology* 24(12):1211–1219; Moret et al., 1997, *J. Neurochem.* 69(2): 815–822; Bel et al., 1999, *Neuropharmacology* 21(6):745–754; and Palmier et al., 1989, *Eur J Clin Pharmacol* 37:235–238.

The NE:5-HT of a particular SNRI also can be calculated using equilibrium dissociation constants ($K_D$'s) for norepinephrine and serotonin transporters as described in Tatsumi et al., 1997, *European Journal of Pharmacology* 340:249–258. For example, a NE>5-HT SNRI compound with a $K_D$ of 2 nM for the norepinephrine transporter and a $K_D$ of 8 nM for the serotonin transporter has an NE:5-HT of 4:1.

Yet another means for determining the NE:5-HT of a particular SNRI involves measuring the affinity ($K_i$) of the SNRI for the norepinephrine and serotonin transporters as described in Owens et al., 1997, *JPET* 283:1305–1322. For example, a NE>5-HT SNRI compound with a $K_i$ of 1 nM for the norepinephrine transporter and a $K_i$ of 20 nM for the serotonin transporter has an NE:5-HT of 20:1.

A specific example of a NE≧5-HT SNRI compound that can be used to practice the present invention is milnacipran. Additional NE≧5-HT SNRI compounds that can be used to practice the present invention include, by way of example and not limitation, any of the aminocyclopropane derivatives disclosed in the following references that inhibit norepinephrine reuptake to an equivalent or greater extent than serotonin reuptake (i.e., that have a NE:5-HT ratio that is ≧1:1): WO95/22521; U.S. Pat. No. 5,621,142; Shuto et al., 1995, *J. Med. Chem.* 38:2964–2968; Shuto et al., 1996, *J. Med. Chem.* 39:4844–4852; Shuto et al., 1998, *J. Med. Chem.* 41:3507–3514; Shuto et al., 2001. *Jpn. J. Pharmacol.* 85:207–213; Noguchi et al., 1999. *Synapse* 31:87–96; and U.S. Pat. No. 4,478,836. All of these references are hereby incorporated herein by reference in their entireties.

In a specific embodiment of the invention, the NE>5-HT SNRI compound is milnacipran. The chemical structure of milnacipran, cis-(±)-2-(aminomethyl)-N,N-diethyl-1-phenyl-ycloropanecarboxamide, is as follows:




Milnacipran is also known in the art as F2207, TN-912, dalcipran, midalcipran, and midalipran. The NE:5-HT of milnacipran is 2:1. See Moret et al., 1985, *Neuropharmacology* 24(12):1211–1219; Palmier et al., 1989, *Eur J Clin Pharmacol* 37:235–238. Milnacipran and methods for its synthesis are described in U.S. Pat. No. 4,478,836, which is hereby incorporated by reference in its entirety. Additional information regarding milnacipran may be found in the Merck Index, 12th Edition, at entry 6281. Quite significantly, milnacipran has been used as an antidepressant in approximately 400,000 patients, and is known to be non-toxic in humans. In clinical trials at dosages of 100 mg/day or 200 mg/day, milnacipran was well tolerated and usually produced no more adverse effects than placebo (Spencer and Wilde, 1998, *Drugs* 56(3):405–427).

Those of skill in the art will recognize that NE≧5-HT SNRI compounds such as milnacipran may exhibit the phenomena of tautomerism, conformational isomerism, geometric isomerism and/or optical isomerism. It should be understood that the invention encompasses any tautomeric, conformational isomeric, optical isomeric and/or geometric isomeric forms of the NE≧5-HT SNRI compounds having one or more of the utilities described herein, as well as mixtures of these various different forms. For example, as is clear from the above structural diagram, milnacipran is optically active. It has been reported in the literature that the dextrogyral enantiomer of milnacipran is about twice as active in inhibiting norepinephrine and serotonin reuptake than the racemic mixture, and that the levrogyral enantiomer is much less potent (see, e.g., Spencer and Wilde, 1998, supra; Viazzo et al., 1996, *Tetrahedron Lett.* 37(26):4519–4522; Deprez et al., 1998, *Eur. J. Drug Metab. Pharmacokinet.* 23(2):166–171). Accordingly, milnacipran may be administered in entantiomerically pure form (e.g., the pure dextrogyral enantiomer) or as a mixture of dextogyral and levrogyral enantiomers, such as a racemic mixture. Unless specifically noted otherwise, the term "milancipran" as used herein refers to both enantiomerically pure forms of milnacipran as well as to mixtures of milnacipran enantiomers. Methods for separating and isolating the dextro- and levrogyral enantiomers of milnacipran and other NE≧5-HT SNRI compounds are well-known (see, e.g., Grard et al., 2000, Electrophoresis 2000 21:3028–3034).

It will also be appreciated that in many instances the NE≧5-HT SNRI compounds may metabolize to produce active NE≧5-HT SNRI compounds. The use of active metabolites is also within the scope of the present invention.

It has been reported that milnacipran and its derivatives have antagonistic properties at the NMDA receptor. See

Shuto et al., 1995, *J. Med. Chem.* 38:2964–2968; Shuto et al., 1996, *J. Med. Chem.* 39:4844–4852; Shuto et al., 1998, *J. Med. Chem.* 41:3507–3514; and Shuto et al., 2001, *Jpn. J. Pharmacol.* 85:207–213. As a consequence, one particularly useful embodiment of the invention includes NE≧5-HT SNRI compounds that also have NMDA antagonistic properties. The NE≧5-HT SNRI compounds with NMDA receptor antagonistic properties can have $IC_{50}$ values from about 1 nM–100 μM. For example, milnacipran has been reported to have an $IC_{50}$ value of about 6.3 μM. The NMDA receptor antagonistic properties of milnacipran and its derivatives are described in Shuto et al., 1995, *J. Med. Chem.*, 38:2964–2968; Shuto et al., 1996, *J. Med. Chem.* 39:4844–4852; Shuto et al., 1998, *J. Med. Chem.* 41:3507–3514; and Shuto et al., 2001, *Jpn. J. Pharmacol.* 85:207–213. Methods for determining the antagonism and affinity for antagonism are disclosed in Shuto et al., 1995, *J. Med. Chem.* 38:2964–2968; Shuto et al., 1996, *J. Med. Chem.* 39:4844–4852; Shuto et al., 1998, *J. Med. Chem.* 41:3507–3514; Noguchi et al., 1999, *Synapse* 31:87–96; and Shuto et al., 2001, *Jpn. J. Pharmacol.* 85:207–213. Aminocyclopropane derivatives disclosed in WO95/22521; U.S. Pat. No. 5,621,142; Shuto et al., 1995, *J. Med. Chem.* 38:2964–2968; Shuto et al., 1996, *J. Med. Chem.* 39:4844–4852; Shuto et al., 1998, *J. Med. Chem.* 41:3507–3514; Noguchi et al., 1999, *Synapse* 31:87–96; and Shuto et al., 2001, *Jpn. J. Pharmacol.* 85:207–213 that inhibit NE reuptake equal to or greater than 5-HT reuptake and have NMDA antagonistic properties can be used to practice the present invention. These references are hereby incorporated by reference in their entirety.

It has recently been reported that compounds that inhibit reuptake of both NE and 5-HT, such as venlafaxine, duloxetine, milnacipran, and certain TCAs, are effective for the treatment of pain, CFS and FMS, among other maladies, when administered in combination with neurotransmitter precursors such as phenylalanine, tyrosine and/or tryptophan. See WO 01/26623. For example, according to one study reported in WO 01/26623, a patient experiencing, inter alia, fatigue and fibromyalgia, was administered many types of drugs, including many types of non-steroidal anti-inflammatories, both tricyclic and serotonin reuptake inhibiting and noradrenalin reuptake inhibiting antidepressants, and even steroids, without effect. When given a combination of lofepramine (70 mg. bd) and L-phenylalanine (500 mg. bd), the patient experienced a considerable improvement in fatigue and fibromyalgia, which persisted for more than six months. Thus, a compound that inhibits reuptake of both NE and 5-HT was effective only when administered in combination with a neurotransmitter precursor.

Quite surprisingly, the present inventors have discovered that the NE≧5-HT SNRI subclass of SNRI compounds are effective in treating CFS, FMS and pain when administered alone (or in combination with other compounds that are not neurotransmitter precursors such as phenylalanine, tyrosine and/or tryptophan, as will be discussed in more detail, below). Thus, in one embodiment of the invention, the NE≧5-HT SNRI compound is administered alone, or in combination with a compound other than a neurotransmitter precursor such as phenylalanine, tyrosine and/or tryptophan.

The NE≧5-HT SNRI compounds, such as, for example, milnacipran, can be administered adjunctively with other active compounds such as antidepressants, analgesics, muscle relaxants, anorectics, stimulants, antiepileptic drugs, and sedative/hypnotics. Specific examples of compounds that can be adjunctively administered with the NE≧5-HT SNRI compounds include, but are not limited to, neurontin, pregabalin, pramipexole, l-DOPA, amphetamine, tizanidine, clonidine, tramadol, morphine, tricyclic antidepressants, codeine, cambamazepine, sibutramine, amphetamine, valium, trazodone and combinations thereof. Typically for FMS patients the NE≧5-HT SNRI compounds may be adjunctively administered with antidepressants, anorectics, analgesics, antiepileptic drugs, muscle relaxants, and sedative/hypnotics. For CFS patients, the NE≧5-HT SNRI compounds may be adjunctively administered antidepressants, anorectics, stimulants, and sedative/hypnotics. For patients suffering from pain the NE≧5-HT SNRI compounds may be adjunctively administered with antidepressants, analgesics, antiepileptic drugs. By adjunctive administration is meant simultaneous administration of the compounds, in the same dosage form, simultaneous administration in separate dosage forms, and separate administration of the compounds. For example, milnacipran can be simultaneously administered with valium, wherein both milnacipran and valium are formulated together in the same tablet. Alternatively, milnacipran could be simultaneously administered with valium, wherein both the milnacipran and valium are present in two separate tablets. In another alternative, milnacipran could be administered first followed by the administration of valium, or vice versa.

The NE≧5-HT SNRI compounds can be administered therapeutically to achieve a therapeutic benefit or prophylactically to achieve a prophylactic benefit. By therapeutic benefit is meant eradication or amelioration of the underlying disorder being treated, e.g., eradication or amelioration of the underlying FMS, CFS or pain disorder, and/or eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that the patient reports an improvement in feeling or condition, notwithstanding that the patient may still be afflicted with the underlying disorder. For example, administration of milnacipran to a patient suffering from FMS provides therapeutic benefit not only when the underlying FMS indication is eradicated or ameliorated, but also when the patient reports decreased fatigue, improvements in sleep patterns, and/or a decrease in the severity or duration of pain.

Although depression is often comorbid in patients suffering from FMS and CFS, and could therefore be characterized as a symptom associated with these disorders, it is well-recognized in the art that NE≧5-HT SNRI compounds such as milnacipran are useful in the treatment of depression. Accordingly, while successful treatment regimens of the invention contemplate providing an improvement in at least one symptom associated with FMS or CFS, treatment regimens that cause an improvement only in depression are considered ineffective for purposes of the present invention. While improvements in associated psychological symptoms such as depression may be reported, for purposes of the present invention, an improvement in the underlying disorder and/or in at least one of the physiological symptoms associated with the disorder must be reported. Thus, the present invention does not contemplate the treatment of depression alone.

For therapeutic administration, the NE≧5-HT SNRI compound typically will be administered to a patient already diagnosed with the particular indication being treated.

For prophylactic administration, the NE≧5-HT SNRI compound may be administered to a patient at risk of developing FMS, CFS, or pain or to a patient reporting one or more of the physiological symptoms of FMS or CFS, even though a diagnosis of FMS or CFS may not have yet been made. Alternatively, prophylactic administration may be applied to avoid the onset of the physiological symptoms

of the underlying disorder, particularly if the symptom manifests cyclically. In this latter embodiment, the therapy is prophylactic with respect to the associated physiological symptoms instead of the underlying indication. For example, the NE≧5-HT SNRI compound could be prophylactically administered prior to bedtime to avoid the sleep disturbances associated with FMS or CFS. Alternatively, the NE≧5-HT SNRI compound could be administered prior to recurrence of pain, or prior to onset of fatigue.

While the invention has been described so far with respect to NE≧5-HT SNRI compounds, the present invention can also be practiced with norepinephrine specific reuptake inhibitors (NARIs). NARIs are a well-recognized class of compounds that specifically inhibit the reuptake of only norepinephrine. An example of a compound that is classified as a NARI is reboxetine.

4.4 Formulation and Routes of Administration

The NE≧5-HT SNRI compounds useful in the present invention, or pharmaceutically acceptable salts thereof, can be delivered to a patient using a wide variety of routes or modes of administration. Suitable routes of administration include, but are not limited to, inhalation, transdermal, oral, rectal, transmucosal, intestinal and parenteral administration, including intramuscular, subcutaneous and intravenous injections.

The term "pharmaceutically acceptable salt" means those salts which retain the biological effectiveness and properties of the compounds used in the present invention, and which are not biologically or otherwise undesirable. Such salts include salts with inorganic or organic acids, such as hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, methanesulfonic acid, p-toluenesulfonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, mandelic acid, malic acid, citric acid, tartaric acid or maleic acid. In addition, if the compounds used in the present invention contain a carboxy group or other acidic group, it may be converted into a pharmaceutically acceptable addition salt with inorganic or organic bases. Examples of suitable bases include sodium hydroxide, potassium hydroxide, ammonia, cyclohexylamine, dicyclohexyl-amine, ethanolamine, diethanolamine and triethanolamine.

The compounds, or pharmaceutically acceptable salts thereof, may be administered singly, in combination with other NE≧5-HT SNRI compounds, and/or in cocktails combined with other therapeutic agents. Of course, the choice of therapeutic agents that can be co-administered with the compounds of the invention will depend, in part, on the condition being treated.

The active NE≧5-HT SNRI compounds (or pharmaceutically acceptable salts thereof) may be administered per se or in the form of a pharmaceutical composition wherein the active compound(s) is in admixture or mixture with one or more pharmaceutically acceptable carriers, excipients or diluents. Pharmaceutical compositions for use in accordance with the present invention may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

For injection, the NE≧5-HT SNRI compounds may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the compounds can be formulated readily by combining the active compound(s) with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained as a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores can be provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

For administration orally, the compounds may be formulated as a sustained release preparation. Numerous techniques for formulating sustained release preparations are described in the following references—U.S. Pat. Nos. 4,891,223; 6,004,582; 5,397,574; 5,419,917; 5,458,005; 5,458,887; 5,458,888; 5,472,708; 6,106,862; 6,103,263; 6,099,862; 6,099,859; 6,096,340; 6,077,541; 5,916,595; 5,837,379; 5,834,023; 5,885,616; 5,456,921; 5,603,956; 5,512,297; 5,399,362; 5,399,359; 5,399,358; 5,725,883; 5,773,025; 6,110,498; 5,952,004; 5,912,013; 5,897,876; 5,824,638; 5,464,633; 5,422,123; and 4,839,177; and WO 98/47491. Specifically, sustained release formulations of milnacipran are described in WO 98/08495. These references are hereby incorporated herein by reference in their entireties.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the active compound(s) may be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and

cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Alternatively, the active compound(s) may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or transcutaneous delivery (for example subcutaneously or intramuscularly), intramuscular injection or a transdermal patch. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

4.5 Effective Dosages

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredient is contained in a therapeutically or prophylactically effective amount, i.e., in an amount effective to achieve therapeutic or prophylactic benefit, as previously discussed. Of course, the actual amount effective for a particular application will depend, inter alia, on the condition being treated and the route of administration. Determination of an effective amount is well within the capabilities of those skilled in the art, especially in light of the disclosure herein.

Therapeutically effective amounts for use in humans can be determined from animal models. For example, a dose for humans can be formulated to achieve circulating concentration that has been found to be effective in animals. Useful animal models of pain are well known in the art. Models of neuropathic pain are described in Zeltser et al., 2000, *Pain* 89:19–24; Bennett et al., 1988, *Pain* 33:87–107; Seltzer et al., 1990, *Pain* 43:205–218; Kim et al., 1992, *Pain* 50:355–363; and Decosterd et al., 2000, *Pain* 87:149–158. An animal model of inflammatory pain using complete Freund's adjuvant is described in Jasmin et al., 1998, *Pain* 75: 367–382. The stress-induced hyperalgesia model described in Quintero et al., 2000, *Pharmacology, Biochemistry and Behavior* 67:449–458 may be used as an animal model of FMS and CFS.

Effective amounts for use in humans can be also be determined from human data for the NE≧5-HT SNRI compounds used to treat depression. The amount administered can be the same amount administered to treat depression or can be an amount lower than the amount administered to treat depression. For example, the amount of milnacipran administered to treat depression is in the range of about 50 mg–400 mg/day. Thus, either 50 mg–400 mg/day or a lower dose can be administered for practicing the present invention.

Patient doses for oral administration of the NE≧5-HT SNRI compound typically range from about 1 μg–1 gm/day. For example, for the treatment of FMS, CFS, or pain with milnacipran the dosage range is typically from 25 mg–400 mg/day, more typically from 100 mg–250 mg/day. The dosage may be administered once per day or several or multiple times per day. The amount of the NE≧5-HT SNRI compound administered to practice methods of the present invention will of course, be dependent on the subject being treated, the severity of the affliction, the manner of administration and the judgment of the prescribing physician. The dose used to practice the invention can produce the desired therapeutic or prophylactic effects, without producing serious side effects.

## 5. EXAMPLES

### 5.1 Example 1

#### Assessment of the Analgesic Properties of Milnacipran in a Rat Pain Model

The rats used in this study are divided into two groups. One group of rats receive a spinal ligation as described in Kim et al., 1992, *Pain* 50(3):355–63 and the other group of rats receive a sham surgery. Each group of rats is further divided into 5 subgroups. Each subgroup receives subcutaneous injection of the vehicle or one of the 4 test doses of milnacipran (5, 10, 25, and 50 mg/kg). The vehicle or milnacipran are administered at a pre-determined time point following the surgeries. Allodynia and thermal hyperalgesia are respectively measured with Von Frey filaments and tail or paw-flick with a radiant heat source. The allodynia and thermal hyperalgesia measurements are performed at the following time points—prior to surgery, following surgery but prior to the administration of vehicle or milnacipran, and following surgery after the administration of vehicle or milnacipran. The allodynia and thermal hyperalgesia measurements will provide information on the ability of milnacipran to block the development of mechanical allodynia and thermal hyperalgesia.

### 5.2 Example 2

#### Assessment of the Efficacy of Milnacipran in an FMS Animal Model

This study is performed on rats or mice that have undergone stress-induced hyperalgesia as described in Quintero et al., 2000, *Pharmacology, Biochemistry and Behavior* 67:449–458. The study consists of 3 groups: placebo, mil-

nacipran subcutaneous pretreatment, and milnacipran treatment. The milnacipran groups are further divided to 4 subgroups and each subgroup is administered 5, 10, 25, or 50 mg/kg of milnacipran. In the milnacipran subcutaneous pretreatment group, the milnacipran is administered prior to the inducement of the stress-induced hyperalgesia. In the milnacipran treatment group, the milnacipran is administered following the inducement of the stress-induced hyperalgesia. Allodynia and thermal hyperalgesia are respectively measured with Von Frey filaments and tail- or paw-flick with a radiant heat source. The allodynia and thermal hyperalgesia measurements are performed at the following time points—prior to both the inducement of stress-induced hyperalgesia and the administration of the milnacipran, prior to the inducement of stress-induced hyperalgesia but following the administration of the milnacipran, following the inducement of stress-induced hyperalgesia but prior to administration of the milnacipran, following both the inducement of stress-induced hyperalgesia and the administration of the milnacipran. The allodynia and thermal hyperalgesia measurements provide information on whether pretreatment or treatment with milnacipran will be effective in the treatment of stress-induced thermal and mechanical hyperalgesia.

### 5.3 Example 3

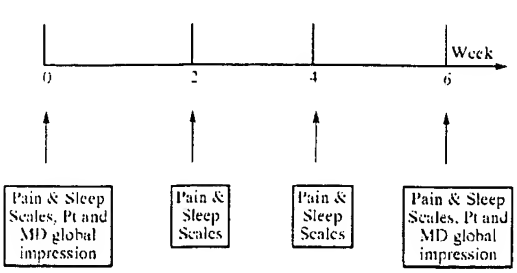
#### Assessment of the Efficacy of Milnacipran in FMS Patients

Approximately 40 subjects are studied for a total of 6 weeks, after being weaned from their previous analgesic or antidepressant medications.

The inclusion criteria for this study is as follows:

1. Patients meet the 1990 American College of Rheumatology criteria for fibromyalgia syndrome.
2. Male or female between the ages of 18 and 70 years. Females are either postmenopausal (no menses for at least 1 year) or status-post oophorectomy (bilateral) or have a negative pregnancy test and be using an accepted method of contraception.
3. Patients have a Gracely intensity pain scale recording (weekly recall) of at least 10 or more on a 20 point scale at baseline.
4. Patients may use non-prescription doses of NSAIDs, aspirin and acetaminophen on a PRN basis for acute pain unrelated to their underlying fibromyalgia.

The patients are divided into 2 groups. The first group is administered 100 mg of milnacipran in a single-dose in the morning, while the second group is administered 50 mg twice a day (i.e., upon awakening and prior to going to sleep). Each patient is then followed for 6 weeks, with visits every two weeks, as follows:




As indicated above, global patient (Pt) and physician (MD) assessments are taken at the beginning and end of the trial. In addition, a total of 4 sets of pain and sleep measures are also performed at 2-week intervals. The pain measure consists of the patient's recall of overall pain over the previous 2-week period as indicated by a 10 cm visual analog scale. The sleep instrument consists of 4 questions taken from the Jenkin's sleep questionnaire. It is expected that milnacipran will produce an improvement in a majority of the patients.

### 5.4 Example 4

#### Assessment of the Efficacy of Milnacipran in Patients with Painful Diabetic Neuropathy

20 patients with painful diabetic neuropathy (DN) are studied in a double-blind cross-over study. The inclusion criteria for the study are—age of between 18 and 85 years, daily pain of at least "moderate intensity" on the Gracely scale for greater than three months that was present more than 50% of the day, and adequate communication ability demonstrated during a telephone conversation and by completion of a pain diary. Additional inclusion criteria are a diagnosis of diabetes, and distal, symmetrical diabetic neuropathy as assessed by either an unequivocal decrease in pinprick, temperature, or vibration sense in both feet or ankles or decreased or absent ankle jerk reflexes. Exclusion criteria are the presence of another more painful condition, difficulty with ambulation, any unstable disease process, a history of significant substance abuse or alcoholism, liver or kidney disease, or concurrent use of a monoamine oxidase inhibitor.

Milnacipran is compared to placebo in a randomized, double-blind, two-period, crossover study. After discontinuing other medication for pain for two weeks, patients enter a one-week baseline period, followed by two six-week drug treatment periods, separated and concluded by a one-week washout period. The treatments, given in random order, are milnacipran titrated up to maximum-tolerated dose or placebo. A nurse calls the patients every three days to titrate medication dosage and to assess pain, side effects, and study compliance. During the first four weeks of each period (titration phase) the medication is increased by 25 mg/day every three days unless the patient reports complete pain relief, side effects that interfere with daily activities, or unless the maximum dose of 200 mg daily is reached. During weeks 5 and 6 (maintenance phase), the highest well-tolerated dose is maintained at a constant level.

Prior to randomization, a general physical exam and laboratory tests (complete blood count, liver function tests, blood glucose, hemoglobin A1c, blood urea nitrogen, creatinine, electrolytes and urinalysis) is obtained. Diabetics are examined to assure they had adequate blood sugar control before and during the trial. They are instructed to perform daily blood sugar monitoring using a fingerstick and a home glucometer. In addition, a neurologic examination is performed at baseline to identify any area of increased pain to pinprick (hyperalgesia), decreased sensation to pinprick, or pain with stimulation by cotton gauze (allodynia); these studies are conducted every 2 weeks during the trial. In addition, patients record their pain intensity in a diary 3 times daily using the Gracely scale. It is expected that milnacipran will produce an improvement in the majority of patients, as measured by both physician neurological exam and patient diary.

Each of the patent applications, patents, publications, and other published documents mentioned or referred to in this specification is herein incorporated by reference in its entirety, to the same extent as if each individual patent application, patent, publication, and other published document was specifically and individually indicated to be incorporated by reference.

While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto.

The invention claimed is:

1. A method of treating pain in an animal subject, comprising administering to an animal subject suffering from pain, an effective amount of milnacipran, or a pharmaceutically acceptable salt thereof, alone or in combination with a compound that is not phenylalanine, tyrosine or tryptophan.

2. The method according to claim 1, wherein the compound is adjunctively administered with antidepressants, analgesics, muscle relaxants, anorectics, stimulants, antiepileptic drugs, sedatives, or hypnotics.

3. The method according to claim 1, wherein the compound is adjunctively administered with neurontin, pregabalin, pramipexole, l-DOPA, amphetamine, tizanidine, clonidine, tramadol, morphine, a tricyclic antidepressant, codeine, carbamazepine, sibutramine, valium, or trazodone.

4. The method according to claim 1, wherein the animal subject is human.

5. The method according to claim 1, wherein the amount administered is from about 25 mg to about 400 mg per day.

6. The method according to claim 1, wherein the compound is formulated in a sustained release dosage formulation.

* * * * *

# EXHIBIT B

United States Patent and Trademark Office



**Assignments on the Web > Patent Query**

# Patent Assignment Abstract of Title

***NOTE:Results display only for issued patents and published applications. For pending or abandoned applications please consult USPTO staff.***

**Total Assignments: 1**

**Patent #:** 6602911 **Issue Dt:** 08/05/2003 **Application #:** 10028547 **Filing Dt:** 12/19/2001

**Publication #:** 20030130353 **Pub Dt:** 07/10/2003

**Inventors:** Jay D. Kranzler, Srinivas G. Rao

**Title:** METHODS OF TREATING FIBROMYALGIA

**Assignment: 1**

**Reel/Frame:** 012773/0222 **Recorded:** 03/27/2002 **Pages:** 4

**Conveyance:** ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

**Assignors:** KRANZLER, JAY D. **Exec Dt:** 03/19/2002

RAO, SRINIVAS G. **Exec Dt:** 03/19/2002

**Assignee:** CYPRESS BIOSCIENCE, INC.
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**Correspondent:** COOLEY GODWARD LLP
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Search Results as of: 03/03/2009 05:01 PM

If you have any comments or questions concerning the data displayed, contact PRD / Assignments at 571-272-3350.
Web interface last modified: October 18, 2008 v.2.0.2

Attorney Docket No: CYPR-023/01US PATENT

**ASSIGNMENT**
**(Joint)**

Jay D. KRANZLER, residing at 7935 Via Capri, La Jolla, CA 92037 and Srinivas G. RAO, residing at 11590 Jaguar Ct., San Diego, CA 92131 (each referred to as "Assignor") have made an invention(s) (the "Invention(s)") set forth in an application for patent of the United States, entitled **METHODS OF TREATING FIBROMYALGIA SYNDROME, CHRONIC FATIGUE SYNDROME AND PAIN**, and which is a:

(1) [] provisional application
  (a) [] to be filed herewith; or
  (b) [] bearing Application No. , and filed on ; or

(2) [X] non-provisional application
  (a) [] to be filed herewith; or
  (b) [X] bearing Application No. 10/028,547, and filed on December 19, 2001.

**WHEREAS**, Cypress Bioscience, Inc., a corporation duly organized under and pursuant to the laws of Delaware, and having its principal place of business at 4350 Executive Drive, Suite #325, San Diego, CA 92121 (the "Assignee"), is desirous of acquiring the entire right, title, and interest in: the Invention(s); the application for patent identified in paragraph (1) or (2); the right to file applications for patent of the United States or other countries on the Invention(s); any application(s) for patent of the United States or other countries claiming priority to these application(s); and any patent(s) of the United States or other countries that may be granted therefor or thereon.

**NOW, THEREFORE**, for good and sufficient consideration, the receipt of which is hereby acknowledged, and to the extent that the Assignor has not done so already via a prior agreement with the Assignee, or if the Assignor has already done so via a prior agreement with the Assignee then in confirmation of any obligation to do so in said prior agreement, the Assignor has sold, assigned, transferred, and set over, and by these presents does sell, assign, transfer, and set over, unto the Assignee, its successors, legal representatives, and assigns, the Assignor's entire right, title, and interest in:

(a) the Invention(s);

(b) the application for patent identified in paragraph (1) or (2);

(c) the right to file applications for patent of the United States or other countries on the Invention(s), including all rights under the Paris Convention for the Protection of Industrial Property and under the Patent Cooperation Treaty;

(d) any application(s) for patent of the United States or other countries claiming the Invention(s);

(e) any application(s) for patent of the United States or other countries claiming priority to the application for patent identified in paragraph (1) or (2) or any application(s) for patent claiming the Invention(s), including any division(s), continuation(s), and continuation(s)-in-part; and

(f) any patent(s) of the United States or other countries that may be granted for or on any application for patent identified in the preceding paragraphs (b) – (e), including any reissue(s) and extension(s) of said patent(s).

The above-granted rights, titles, and interests are to be held and enjoyed by the Assignee, for its own use and behalf and the use and behalf of its successors, legal representatives, and assigns, as fully and entirely as the same would have been held and enjoyed by the Assignor had this sale and assignment not been made.

The Assignor hereby represents to the Assignee, its successors, legal representatives, and assigns, that, at the time of execution and delivery of these presents, or if applicable, at such time said prior agreement was executed, the Assignor is a lawful owner of an undivided interest in the entire right, title, and interest in and to the Invention(s), that the Invention(s) are unencumbered, except, if applicable, by obligation to assign in accordance with said prior agreement, and that the Assignor has good and full right and lawful authority to sell and convey the same in the manner set forth herein.

The Assignor hereby covenants and agrees to and with the Assignee, its successors, legal representatives, and assigns, that the Assignor will sign all papers and documents, take all lawful oaths, and do all acts necessary or required to be done in connection with any and all proceedings for the procurement, maintenance, enforcement and defense of the Invention(s), said applications, and said patents, including interference proceedings, without charge to the Assignee, its successors, legal representatives, and assigns, but at the cost and expense of the Assignee, its successors, legal representatives, and assigns.

The Assignor hereby authorizes and requests the attorneys of COOLEY GODWARD L.L.P. to insert in the spaces provided above the filing date, the application number, and the attorney docket number of the application identified in paragraph (1) or (2) when known.

The Assignor hereby requests the Commissioner of Patents to issue said patents of the United States to the Assignee for the sole use and behalf of the Assignee, its successors, legal representatives, and assigns.

Date: March 19, 2002 By: Jay D. KRANZLER

State of California )
ss.
County of San Diego )

On March 19, 2002, before me, Manda S. Hall, Notary Public, personally appeared Jay Kranzler, personally known to me or proved to me on the basis of satisfactory evidence, to be the person(s) whose name(s) is/are subscribed to the within instrument and acknowledged to me that he/she/they executed the same in his/her/their authorized capacity(ies), and that by his/her/their signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

WITNESS my hand and official seal.

Manda S. Hall
Signature of Notary Public

MANDA S. HALL
Commission # 1335854
Notary Public - California
San Diego County
My Comm. Expires Jan 12, 2006
Place Notary Seal Above

Date: March 19, 2002 By: Srinivas G. RAO

State of California )
ss.
County of San Diego )

On March 19, 2002, before me, Manda S. Hall, Notary Public, personally appeared Srinivas Rao, personally known to me or proved to me on the basis of satisfactory evidence, to be the person(s) whose name(s) is/are subscribed to the within instrument and acknowledged to me that he/she/they executed the same in his/her/their authorized capacity(ies), and that by his/her/their signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

WITNESS my hand and official seal.

Manda S. Hall
Signature of Notary Public

MANDA S. HALL
Commission # 1335854
Notary Public - California
San Diego County
My Comm. Expires Jan 12, 2006
Place Notary Seal Above

# EXHIBIT C

PATENT
Attorney Docket No. 11013.0001-00000

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent of: )
)
Jay D. KRANZLER et al. )
)
Patent No. 6,992,110 )
)
Issued: January 31, 2006 )
)
For: METHODS OF TREATING )
FIBROMYALGIA SYNDROME, )
CHRONIC FATIGUE SYNDROME )
AND PAIN )

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

**REVOCATION OF POWER OF ATTORNEY**
**STATEMENT UNDER 37 C.F.R. § 3.73(b)**
**AND GRANT OF NEW POWER OF ATTORNEY**

The undersigned, a representative authorized to sign on behalf of the assignee owning all of the interest in this patent, hereby revokes all previous powers of attorney or authorization of agent granted in this patent before the date of execution hereof.

As required by 37 C.F.R. § 3.73(b), the undersigned verifies that Cypress Bioscience, Inc. is the assignee of the entire right, title, and interest in the patent identified above by virtue of an assignment from the inventors recorded in parent Application No. 10/028,547 at the U.S. Patent and Trademark Office at Reel 012773, Frame 0222.

The undersigned representative of the Assignee hereby grants its power of attorney to the patent practitioners associated with **FINNEGAN, HENDERSON,**

**FARABOW, GARRETT & DUNNER, L.L.P., Customer Number 22,852,** to transact all business in the Patent and Trademark Office connected with this patent.

Please send all future correspondence concerning this patent to Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P., Customer No. 22,852.

Dated: March 4, 2009

By: _____

Srinivas Rao, M.D., Ph.D.
Chief Scientific Officer
Cypress Bioscience, Inc.

# EXHIBIT D

**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use Savella safely and effectively. See full prescribing information for Savella.**
**Savella (milnacipran HCl) Tablets**
**Initial U.S. Approval: 2009**

**WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS**
***See full prescribing information for complete boxed warning.***

- **Increased risk of suicidal ideation, thinking and behavior in children, adolescents, and young adults taking antidepressants for major depressive disorder (MDD) and other psychiatric disorders. Savella is not approved for use in pediatric patients (5.1)**

**----------INDICATIONS AND USAGE----------**
Savella™ is a selective serotonin and norepinephrine reuptake inhibitor (SNRI) indicated for the management of fibromyalgia (1)
Savella is not approved for use in pediatric patients (5.1)

**----------DOSAGE AND ADMINISTRATION----------**

- Administer Savella in two divided doses per day (2.1)
- Begin dosing at 12.5 mg on the first day and increase to 100 mg/day over a 1-week period (2.1):
  Day 1: 12.5 mg once
  Days 2-3: 25 mg/day (12.5 mg twice daily)
  Days 4-7: 50 mg/day (25 mg twice daily)
  After Day 7: 100 mg/day (50 mg twice daily)
- Recommended dose is 100 mg/day (2.1)
- May be increased to 200 mg/day based on individual patient response (2.1)
- Dose should be adjusted in patients with severe renal impairment (2.2)

**----------DOSAGE FORMS AND STRENGTHS----------**

- Tablets: 12.5 mg, 25 mg, 50 mg, 100 mg (3)

**----------CONTRAINDICATIONS----------**

- Use of monoamine oxidase inhibitors concomitantly or in close temporal proximity (4.1)
- Use in patients with uncontrolled narrow-angle glaucoma (4.2)

**----------WARNINGS AND PRECAUTIONS----------**

- Suicidality: Monitor for worsening of depressive symptoms and suicide risk (5.1)
- Serotonin Syndrome: Serotonin syndrome has been reported with SNRIs and SSRIs. Concomitant use of serotonergic drugs is not recommended (5.2)
- Elevated blood pressure and heart rate: Cases have been reported with Savella. Monitor blood pressure and heart rate prior to initiating treatment with Savella and periodically throughout treatment (5.3, 5.4)
- Seizures: Cases have been reported with Savella therapy. Prescribe Savella with care in patients with a history of seizure disorder. (5.5)
- Hepatotoxicity: More patients treated with Savella than with placebo experienced mild elevations of ALT and AST. Rarely, fulminant hepatitis has been reported in patients treated with Savella. Avoid concomitant use of Savella in patients with substantial alcohol use or chronic liver disease (5.6)
- Discontinuation: Withdrawal symptoms have been reported in patients when discontinuing treatment with Savella. A gradual dose reduction is recommended (5.7)
- Abnormal Bleeding: Savella may increase the risk of bleeding events. Caution patients about the risk of bleeding associated with the concomitant use of Savella and NSAIDs, aspirin, or other drugs that affect coagulation. (5.9)
- Male patients with a history of obstructive uropathies may experience higher rates of genitourinary adverse events (5.11)

**----------ADVERSE REACTIONS----------**
The most frequently occurring adverse reactions (≥ 5% and greater than placebo) were nausea, headache, constipation, dizziness, insomnia, hot flush, hyperhidrosis, vomiting, palpations, heart rate increased, dry mouth, and hypertension (6.3).

**To report SUSPECTED ADVERSE REACTIONS, contact Forest Pharmaceuticals, Inc., at (800) 678-1605 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

**----------DRUG INTERACTIONS----------**

- Savella is unlikely to be involved in clinically significant pharmacokinetic drug interactions (7)
- Pharmacodynamic interactions of Savella with other drugs can occur (7)

**----------USE IN SPECIFIC POPULATIONS----------**

- Pregnancy and nursing mothers: Use only if the potential benefit justifies the potential risk to the fetus or child. (8.1, 8.3)

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**

**Revised: January 2009**

**FULL PRESCRIBING INFORMATION: CONTENTS***



*Sections or subsections omitted from the full prescribing information are not listed.

**WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS Savella is a selective serotonin and norepinephrine reuptake inhibitor (SNRI), similar to some drugs used for the treatment of depression and other psychiatric disorders. Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of such drugs in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on Savella should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Savella is not approved for use in the treatment of major depressive disorder. Savella is not approved for use in pediatric patients [*see Warnings and Precautions (5.1), Use in Specific Populations (8.4)*]**

## 1 INDICATIONS AND USAGE

Savella is indicated for the management of fibromyalgia.

Savella is not approved for use in pediatric patients [*see Use in Specific Populations (8.4)*].

## 2 DOSAGE AND ADMINISTRATION

Savella is given orally with or without food.
Taking Savella with food may improve the tolerability of the drug.

### 2.1 Recommended Dosing

The recommended dose of Savella is 100 mg/day (50 mg twice daily).

Dosing should be titrated according to the following schedule:
**Day 1:** 12.5 mg once
**Days 2-3:** 25 mg/day (12.5 mg twice daily)
**Days 4-7:** 50 mg/day (25 mg twice daily)
**After Day 7:** 100 mg/day (50 mg twice daily)

Based on individual patient response, the dose may be increased to 200 mg/day (100 mg twice daily).

Doses above 200 mg/day have not been studied.

Savella should be tapered and not abruptly discontinued after extended use *[see Discontinuing Savella (2.4) and Warnings and Precautions (5.7)]*

### 2.2 Patients with Renal Insufficiency

No dosage adjustment is necessary in patients with mild renal impairment.
Savella should be used with caution in patients with moderate renal impairment.
For patients with severe renal impairment (indicated by an estimated creatinine clearance of 5-29 mL/min), the maintenance dose should be reduced by 50% to 50 mg/day (25 mg twice daily).

Based on individual patient response, the dose may be increased to 100 mg/day (50 mg twice daily).
Savella is not recommended for patients with end-stage renal disease.

### 2.3 Patients with Hepatic Insufficiency

No dosage adjustment is necessary for patients with hepatic impairment.
As with any drug, caution should be exercised in patients with severe hepatic impairment.

### 2.4 Discontinuing Savella

Withdrawal symptoms have been observed in clinical trials following discontinuation of milnacipran, as with other serotonin and norepinephrine re-uptake inhibitors (SNRIs) and selective serotonin re-uptake inhibitors (SSRIs). Patient should be monitored for these symptoms when discontinuing treatment. Savella should be tapered and not abruptly discontinued after extended use [*see Warnings and Precautions (5.7)*].

### 2.5 Switching patients to or from a Monoamine Oxidase Inhibitor (MAOI)

At least 14 days should elapse between discontinuation of a MAOI and initiation of therapy with Savella. In addition, at least 5 days should be allowed after stopping Savella before starting a MAOI [*see Contraindications (4.1)*].

## 3 DOSAGE FORMS AND STRENGTHS

Film-coated, immediate release tablets in four strengths: 12.5 mg, 25 mg, 50 mg, and 100 mg of milnacipran hydrochloride.
12.5 mg tablets are round, pink, "F" on one side, "L" on the reverse;
25 mg tablets are round, white, "FL" on one side, "25" on the reverse;
50 mg tablets are oval, green, "FL" on one side, "50" on the reverse;
100 mg tablets are oval, blue, "FL" on one side, "100" on the reverse
[*see Description* (11) *and How Supplied/ Storage and Handling (16)*].

## 4 CONTRAINDICATIONS

### 4.1 Monoamine Oxidase Inhibitors

Concomitant use of Savella in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated. In patients receiving a serotonin reuptake inhibitor in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued serotonin reuptake inhibitors and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. The effects of combined use of Savella and MAOIs have not been evaluated in humans. Therefore, it is recommended that Savella should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 5 days should be allowed after stopping Savella before starting an MAOI [see *Dosage and Administration (2.5), Warnings and Precautions* (5.2)].

### 4.2 Uncontrolled Narrow-Angle Glaucoma

In clinical trials, Savella was associated with an increased risk of mydriasis. Mydriasis has been reported with other dual reuptake inhibitors of norepinephrine and serotonin; therefore, do not use Savella in patients with uncontrolled narrow-angle glaucoma.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Suicide Risk

Savella is a selective serotonin and norepinephrine re-uptake inhibitor (SNRI), similar to some drugs used for the treatment of depression and other psychiatric disorders.

Patients, both adult and pediatric, with depression or other psychiatric disorders may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking these medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants, including drugs that inhibit the reuptake of norepinephrine and/or serotonin, may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment.

In the placebo-controlled clinical trials of adults with fibromyalgia, among the patients who had a history of depression at treatment initiation, the incidence of suicidal ideation was 0.5% in patients treated with placebo, 0% in patients treated with Savella 100 mg/day, and 1.3% in patients treated with Savella 200 mg/day. No suicides occurred in the short-term or longer-term (up to 1 year) fibromyalgia trials.

Pooled analyses of short-term placebo-controlled trials of drugs used to treat depression (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior

(suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with these drugs compared to placebo in adults beyond age 24; there was a reduction in suicidality risk with antidepressants compared to placebo in adults age 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 drugs used to treat depression in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk of differences (drug versus placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

**Table 1. Risk Differences (Drug – Placebo) in the number of Cases of Suicidality, per 1000 patients treated**

| Age Range | Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated |
|---|---|
| < 18 | 14 additional cases |
| 18-24 | 5 additional cases |
| | **Decreases Compared to Placebo** |
| 25-64 | 1 fewer case |
| ≥ 65 | 6 fewer cases |

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

**All patients being treated with drugs inhibiting the reuptake of norepinephrine and/or serotonin for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.**

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, have been reported in adult and pediatric patients being treated with drugs inhibiting the reuptake of norepinephrine and/or serotonin for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients who may experience worsening depressive symptoms,

or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe or abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment due to worsening depressive symptoms or emergent suicidality, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can produce withdrawal symptoms *[see Dosage and Administration—Recommended Dosing (2.1), Dosage—Discontinuing Savella (*2.4), and *Warnings and Precautions—Discontinuation of Treatment with Savella (*5.7*)]*.

**Families and caregivers of patients being treated with drugs inhibiting the reuptake of norepinephrine and/or serotonin for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Savella should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.**

**5.2 Serotonin Syndrome**

The development of a potentially life-threatening serotonin syndrome may occur with agents that inhibit serotonin reuptake, including Savella, particularly with concomitant use of serotonergic drugs (including triptans and tramadol) and with drugs which impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

The concomitant use of Savella with MAOIs is contraindicated *[see Contraindications (4.1)]*.

If concomitant treatment of Savella with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases *[see Drug Interactions (7)]*.

The concomitant use of Savella with serotonin precursors (such as tryptophan) is not recommended *[see Drug Interactions (7)]*.

**5.3 Effects on Blood Pressure**

Inhibition of the reuptake of norepinephrine (NE) and serotonin (5-HT) can lead to cardiovascular effects. SNRIs, including Savella, have been associated with reports of increase in blood pressure.

In a double-blind, placebo-controlled clinical pharmacology study in healthy subjects designed to evaluate the effects of milnacipran on various parameters, including blood pressure at supratherapeutic doses, there was evidence of mean increases in supine blood pressure at doses up to 300 mg twice daily (600 mg/day). At the highest 300 mg twice daily dose, the mean increase in systolic blood pressure was up to 8.1 mm Hg for the placebo group and up to 10.0 mm Hg for the Savella treated group over the 12 hour steady state dosing interval. The corresponding mean increase in diastolic blood pressure over this interval was up to 4.6 mm Hg for placebo and up to 11.5 mm Hg for the Savella treated group.

In the 3-month placebo-controlled fibromyalgia clinical trials, Savella treatment was associated with mean increases of up to 3.1 mm Hg in systolic blood pressure (SBP) and diastolic blood pressure (DBP) [*see Adverse Reactions (6.3)*].

In the placebo-controlled trials, among fibromyalgia patients who were non-hypertensive at baseline, approximately twice as many patients in the Savella treatment arms became hypertensive at the end of the study (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg) compared with the placebo patients: 7.2% of patients in the placebo arm versus 19.5% of patients treated with Savella 100 mg/day and 16.6% of patients treated with Savella 200 mg/day. Among patients who met systolic criteria for pre-hypertension at baseline (SBP 120-139 mmHg), more patients became hypertensive at the end of the study in the Savella treatment arms than placebo: 9% of patients in the placebo arm versus 14% in both the Savella 100 mg/day and the Savella 200 mg/day treatment arms.

Among fibromyalgia patients who were hypertensive at baseline, more patients in the Savella treatment arms had a >15 mmHg increase in SBP than placebo at the end of the study: 1% of patients in the placebo arm versus 7% in the Savella 100 mg/day and 2% in the Savella 200 mg/day treatment arms. Similarly, more patients who were hypertensive at baseline and were treated with Savella had DBP increases > 10 mmHg than placebo at the end of study: 3% of patients in the placebo arm versus 8% in the Savella 100 mg/day and 6% in the Savella 200 mg/day treatment arms.

Sustained increases in SBP (increase of ≥ 15 mmHg on three consecutive post-baseline visits) occurred in 2% of placebo patients versus 9% of patients receiving Savella 100 mg/day and 6% of patients receiving Savella 200 mg/day. Sustained increases in DBP (increase of ≥ 10 mmHg on 3 consecutive post-baseline visits) occurred in 4% of patients receiving placebo versus 13% of patients receiving Savella 100 mg/day and 10% of patients receiving Savella 200 mg/day.

Sustained increases in blood pressure could have adverse consequences. Cases of elevated blood pressure requiring immediate treatment have been reported.

Concomitant use of Savella with drugs that increase blood pressure and pulse has not been evaluated and such combinations should be used with caution *[see Drug Interactions (7)]*.

Effects of Savella on blood pressure in patients with significant hypertension or cardiac disease have not been systematically evaluated. Savella should be used with caution in these patients.

Blood pressure should be measured prior to initiating treatment and periodically measured throughout Savella treatment. Pre-existing hypertension and other cardiovascular disease should be treated before starting therapy with Savella. For patients who experience a sustained increase in blood pressure while receiving Savella, either dose reduction or discontinuation should be considered.

**5.4 Effects on Heart Rate**

SNRIs have been associated with reports of increase in heart rate.

In clinical trials, relative to placebo, Savella treatment was associated with mean increases in pulse rate of approximately 7 to 8 beats per minute [*see Adverse Reactions (6.2,6.3)*].

Increases in pulse ≥ 20 bpm occurred more frequently in Savella-treated patients when compared to placebo: 0.3% in the placebo arm versus 8% in the Savella 100 mg/day and 8% in the 200 mg/day treatment arms. The effect of Savella on heart rate did not appear to increase with increasing dose.

Savella has not been systematically evaluated in patients with a cardiac rhythm disorder.

Heart rate should be measured prior to initiating treatment and periodically measured throughout Savella treatment. Pre-existing tachyarrhythmias and other cardiac disease should be treated before starting therapy with Savella. For patients who experience a sustained increase in heart rate while receiving Savella, either dose reduction or discontinuation should be considered.

**5.5 Seizures**
Savella has not been systematically evaluated in patients with a seizure disorder. In clinical trials evaluating Savella in patients with fibromyalgia, seizures/convulsions have not been reported. However, seizures have been reported infrequently in patients treated with Savella for disorders other than fibromyalgia. Savella should be prescribed with care in patients with a history of a seizure disorder.

**5.6 Hepatotoxicity**
In the placebo-controlled fibromyalgia trials, increases in the number of patients treated with Savella with mild elevations of ALT or AST (1-3 times the upper limit of normal, ULN) were observed. Increases in ALT were more frequently observed in the patients treated with Savella 100 mg/day (6%) and Savella 200 mg/day (7%), compared to the patients treated with placebo (3%). One patient receiving Savella 100 mg/day (0.2%) had an increase in ALT greater than 5 times the upper limit of normal but did not exceed 10 times the upper limit of normal. Increases in AST were more frequently observed in the patients treated with Savella 100 mg/day (3%) and Savella 200 mg/day (5%) compared to the patients treated with placebo (2%).

The increases of bilirubin observed in the fibromyalgia clinical trials were not clinically significant. No case met the criteria of elevated ALT > 3x ULN and associated with an increase in bilirubin ≥ 2x ULN.

There have been cases of increased liver enzymes and reports of severe liver injury, including fulminant hepatitis with milnacipran from foreign postmarketing experience. In the cases of severe liver injury there were significant underlying clinical conditions and/or the use of multiple concomitant medications. Because of underreporting, it is impossible to provide an accurate estimate of the true incidence of these reactions.

Savella should be discontinued in patients who develop jaundice or other evidence of liver dysfunction. Treatment with Savella should not be resumed unless another cause can be established.

Savella should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

**5.7 Discontinuation of Treatment with Savella**
Withdrawal symptoms have been observed in clinical trials following discontinuation of milnacipran, as with other SNRIs and SSRIs.

During marketing of milnacipran, and other SNRIs and SSRIs, there have been spontaneous reports of adverse events indicative of withdrawal and physical dependence occurring upon discontinuation of these drugs, particularly when discontinuation is abrupt. The adverse events include the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Although these events are generally self-limiting, some have been reported to be severe.

Patients should be monitored for these symptoms when discontinuing treatment with Savella. Savella should be tapered and not abruptly discontinued after extended use. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate *[see Dosage and Administration (2.4)]*.

**5.8 Hyponatremia**
Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Savella. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SNRIs, SSRIs, or Savella. Also, patients taking diuretics or who are otherwise volume-depleted may be at greater risk [*see Geriatric Use (8.5)*]. Discontinuation of Savella should be considered in patients with symptomatic hyponatremia.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

**5.9 Abnormal Bleeding**
SSRIs and SNRIs, including Savella, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anti-coagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of Savella and NSAIDs, aspirin, or other drugs that affect coagulation.

**5.10 Activation of Mania**
No activation of mania or hypomania was reported in the clinical trials evaluating effects of Savella in patients with fibromyalgia. However those clinical trials excluded patients with current major depressive episode. Activation of mania and hypomania have been reported in patients with mood disorders who were treated with other similar drugs for major depressive disorder. As with these other agents, Savella should be used cautiously in patients with a history of mania.

**5.11 Patients with a History of Dysuria**
Because of their noradrenergic effect, SNRIs including Savella, can affect urethral resistance and micturition. In the controlled fibromyalgia trials, dysuria occurred more frequently in patients treated with Savella (1%) than in placebo-treated patients (0.5%). Caution is advised in use of Savella in patients with a history of dysuria, notably in male patients with prostatic hypertrophy, prostatitis, and other lower urinary tract obstructive disorders. Male patients are more prone to genitourinary adverse effects, such as dysuria or urinary retention, and may experience testicular pain or ejaculation disorders.

**5.12 Controlled Narrow-Angle Glaucoma**
Mydriasis has been reported in association with SNRIs and Savella; therefore, Savella should be used cautiously in patients with controlled narrow-angle glaucoma.
Do not use Savella in patients with Uncontrolled Narrow-Angle Glaucoma *[see Contraindications (4.2)]*.

### 5.13 Concomitant Use with Alcohol
In clinical trials, more patients treated with Savella developed elevated transaminases than did placebo treated patients [see *Warnings and Precautions (5.6)*]. Because it is possible that milnacipran may aggravate pre-existing liver disease, Savella should not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

### 5.14 Allergy to FD&C Yellow No. 5
This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

## 6 ADVERSE REACTIONS

### 6.1 Clinical Trial Data Sources
Savella was evaluated in three double-blind placebo-controlled trials involving 2209 fibromyalgia patients (1557 patients treated with Savella and 652 patients treated with placebo) for a treatment period up to 29 weeks.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse reaction of the type listed. A reaction was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

### 6.2 Adverse Reactions Leading to Discontinuation
In placebo-controlled trials in patients with fibromyalgia, 23% of patients treated with Savella 100 mg/day, 26% of patients treated with Savella 200 mg/day discontinued prematurely due to adverse reactions, compared to 12% of patients treated with placebo. The adverse reactions that led to withdrawal in ≥ 1% of patients in the Savella treatment group and with an incidence rate greater than that in the placebo treatment group were nausea (milnacipran 6%, placebo 1%), palpitations (milnacipran 3%, placebo 1%), headache (milnacipran 2%, placebo 0%), constipation (milnacipran 1%, placebo 0%), heart rate increased (milnacipran 1%, placebo 0%), and hyperhidrosis (milnacipran 1%, placebo 0%), vomiting (milnacipran 1%, placebo 0%), and dizziness (milnacipran 1% and placebo 0.5%). Discontinuation due to adverse reactions was generally more common among patients treated with Savella 200 mg/day compared to Savella 100 mg/day.

### 6.3 Most Common Adverse Reactions
In the placebo-controlled fibromyalgia patient trials the most frequently occurring adverse reaction in clinical trials was nausea. The most common adverse reactions (incidence ≥ 5% and twice placebo) in patients treated with Savella were constipation, hot flush, hyperhidrosis, vomiting, palpitations, heart rate increased, dry mouth, and hypertension.

Table 2 lists all adverse reactions that occurred in at least 2% of patients treated with Savella at either 100 or 200 mg/day and at an incidence greater than that of placebo.

| Table 2. Treatment-Emergent Adverse Reaction Incidence in Placebo Controlled Trials in Fibromyalgia Patients (Events Occurring in at Least 2% of All Savella-Treated Patients and Occurring More Frequently in Either Savella Treatment Group Than in the Placebo Treatment Group) | | | | |
|---|---|---|---|---|
| **System Organ Class– Preferred Term** | **Savella 100 mg/day (n = 623) %** | **Savella 200 mg/day (n = 934) %** | **All Savella (n = 1557) %** | **Placebo (n = 652) %** |
| **Cardiac Disorders** | | | | |
| Palpitations | 8 | 7 | 7 | 2 |
| Tachycardia | 3 | 2 | 2 | 1 |
| **Eye Disorders** | | | | |
| Vision blurred | 1 | 2 | 2 | 1 |
| **Gastrointestinal Disorders** | | | | |
| Nausea | 35 | 39 | 37 | 20 |
| Constipation | 16 | 15 | 16 | 4 |
| Vomiting | 6 | 7 | 7 | 2 |
| Dry mouth | 5 | 5 | 5 | 2 |
| Abdominal pain | 3 | 3 | 3 | 2 |
| **General Disorders** | | | | |
| Chest pain | 3 | 2 | 2 | 2 |
| Chills | 1 | 2 | 2 | 0 |
| Chest discomfort | 2 | 1 | 1 | 1 |
| **Infections** | | | | |
| Upper respiratory tract infection | 7 | 6 | 6 | 6 |
| **Investigations** | | | | |
| Heart rate increased | 5 | 6 | 6 | 1 |
| Blood pressure increased | 3 | 3 | 3 | 1 |
| **Metabolism and Nutrition Disorders** | | | | |
| Decreased appetite | 1 | 2 | 2 | 0 |
| **Nervous System Disorders** | | | | |
| Headache | 19 | 17 | 18 | 14 |
| Dizziness | 11 | 10 | 10 | 6 |
| Migraine | 6 | 4 | 5 | 3 |
| Paresthesia | 2 | 3 | 2 | 2 |
| Tremor | 2 | 2 | 2 | 1 |
| Hypoesthesia | 1 | 2 | 1 | 1 |
| Tension headache | 2 | 1 | 1 | 1 |
| **Psychiatric Disorders** | | | | |
| Insomnia | 12 | 12 | 12 | 10 |
| Anxiety | 5 | 3 | 4 | 4 |
| **Respiratory Disorders** | | | | |
| Dyspnea | 2 | 2 | 2 | 1 |
| **Skin Disorders** | | | | |
| Hyperhidrosis | 8 | 9 | 9 | 2 |
| Rash | 3 | 4 | 3 | 2 |
| Pruritus | 3 | 2 | 2 | 2 |
| **Vascular Disorders** | | | | |
| Hot flush | 11 | 12 | 12 | 2 |
| Hypertension | 7 | 4 | 5 | 2 |
| Flushing | 2 | 3 | 3 | 1 |

**6.4 Weight Changes**
In placebo-controlled fibromyalgia clinical trials, patients treated with Savella for up to 3 months experienced a mean weight loss of approximately 0.8 kg in both the Savella 100 mg/day and the Savella 200 mg/day treatment groups, compared with a mean weight loss of approximately 0.2 kg in placebo-treated patients.

**6.5 Genitourinary Adverse Reactions in Males**
In the placebo-controlled fibromyalgia studies, the following treatment-emergent adverse reactions related to the genitourinary system were observed in at least 2% of male patients treated with Savella, and occurred at a rate greater than in placebo-treated male patients: dysuria, ejaculation disorder, erectile dysfunction, ejaculation failure, libido decreased, prostatitis, scrotal pain, testicular pain, testicular swelling, urinary hesitation, urinary retention, urethral pain, and urine flow decreased.

**6.6 Other Adverse Reactions Observed During Clinical Trials of Savella in Fibromyalgia**
Following is a list of frequent (those occurring on one or more occasions in at least 1/100 patients) treatment-emergent adverse reactions reported from 1824 fibromyalgia patients treated with Savella for periods up to 68 weeks. The listing does not include those events already listed in Table 1, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life threatening.

Adverse reactions are categorized by body system and listed in order of decreasing frequency. Adverse reactions of major clinical importance are described in the *Warnings and Precautions* section (5).

Gastrointestinal Disorders — diarrhea, dyspepsia, gastroesophageal reflux disease, flatulence, abdominal distension
General Disorders — fatigue, peripheral edema, irritability, pyrexia
Infections — urinary tract infection, cystitis
Injury, Poisoning, and Procedural Complications — contusion, fall
Investigations — weight decreased or increased
Metabolism and Nutrition Disorders — hypercholesterolemia
Nervous System Disorders — somnolence, dysgeusia
Psychiatric Disorders — depression, stress
Skin Disorders — night sweats

**6.7 Postmarketing Spontaneous Reports**
The following additional adverse reactions have been identified from spontaneous reports of Savella received worldwide. These adverse reactions have been chosen for inclusion because of a combination of seriousness, frequency of reporting, or potential causal connection to Savella. However, because these adverse reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events include:

Blood and Lymphatic System Disorders — leukopenia, neutropenia, thrombocytopenia
Cardiac Disorders — supraventricular tachycardia
Eye Disorders — accommodation disorder
Endocrine Disorders — hyperprolactinemia
Hepatobiliary Disorders — hepatitis
Metabolism and Nutrition Disorders — anorexia, hyponatremia
Musculoskeletal and Connective Tissue Disorders — rhabdomyolysis

Nervous System Disorders — convulsions (including grand mal), loss of consciousness, neuroleptic malignant syndrome, Parkinsonism, serotonin syndrome
Psychiatric Disorders — delirium, hallucination
Renal and Urinary Disorders — acute renal failure
Reproductive System and Breast Disorders — galactorrhea
Skin Disorders — erythema multiforme, Stevens Johnson syndrome
Vascular Disorders — hypertensive crisis

## 7 DRUG INTERACTIONS

Milnacipran undergoes minimal CYP450 related metabolism, with the majority of the dose excreted unchanged in urine (55%), and has a low binding to plasma proteins (13%). In vitro and in vivo studies showed that Savella is unlikely to be involved in clinically significant pharmacokinetic drug interactions *[see Pharmacokinetics in Special Populations (12.4)]*.

### Clinically Important Interactions with Other Drugs

*Lithium*: Serotonin syndrome may occur when lithium is co-administered with Savella and with other drugs that impair metabolism of serotonin [*see Warnings and Precautions – Serotonin Syndrome (5.2)*].
*Epinephrine and norepinephrine*: Savella inhibits the reuptake of norepinephrine. Therefore concomitant use of Savella with epinephrine and norepinephrine may be associated with paroxysmal hypertension and possible arrhythmia [*see Warnings and Precautions – Effects on Blood Pressure (5.3)* and *Effects on Heart Rate (5.4)*]
*Serotonergic Drugs:* Co-administration of Savella with other inhibitors of serotonin re-uptake may result in hypertension and coronary artery vasoconstriction, through additive serotonergic effects *[see Warnings and Precautions (5.2)]*.
*Digoxin*: Use of Savella concomitantly with digoxin may be associated with potentiation of adverse hemodynamic effects. Postural hypotension and tachycardia have been reported in combination therapy with intravenously administered digoxin (1 mg). Co-administration of Savella and intravenous digoxin should be avoided [*see Warnings and Precautions (5.3, 5.4)*]
*Clonidine*: Because Savella inhibits norepinephrine reuptake, co-administration with clonidine may inhibit clonidine's anti-hypertensive effect.
*Clomipramine*: In a drug-drug interaction study, an increase in euphoria and postural hypotension was observed in patients who switched from clomipramine to Savella.
*CNS-active drugs:* Given the primary CNS effects of Savella, caution should be used when it is taken in combination with other centrally acting drugs, including those with a similar mechanism of action.
*Monoamine Oxidase Inhibitors (MAOIs):* [*see Contraindications (4.1)*].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category C
Milnacipran increased the incidence of dead fetuses in utero in rats at doses of 5 mg/kg/day (0.25 times the MRHD on a mg/m$^2$ basis). Administration of milnacipran to mice and rabbits during the period of organogenesis did not result in embryotoxicity or teratogenicity at doses up to 125 mg/kg/day in mice (3 times the maximum recommended human dose [MRHD] of 200 mg/day on a mg/m$^2$ basis) and up to 60 mg/kg/day in rabbits (6 times the MRHD of 200 mg/day on a mg m$^2$ basis). In rabbits, the incidence of the skeletal variation, extra single rib, was increased following administration of milnacipran at 15 mg/kg/day during the period of organogenesis.

There are no adequate and well-controlled studies in pregnant women. Savella should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects
Neonates exposed to dual reuptake inhibitors of serotonin and norepinephrine, or selective serotonin reuptake inhibitors late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of these classes of drugs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [*see Warnings and Precautions (5.2)*].

In rats, a decrease in pup body weight and viability on postpartum day 4 were observed when milnacipran, at a dose of 5 mg/kg/day (approximately 0.2 times the MRHD on a mg/m$^2$ basis), was administered orally to rats during late gestation. The no-effect dose for maternal and offspring toxicity was 2.5 mg/kg/day (approximately 0.1 times the MRHD on a mg/m$^2$ basis).

**8.2 Labor and Delivery**
The effect of milnacipran on labor and delivery is unknown. The use of Savella during labor and delivery is not recommended.

**8.3 Nursing Mothers**
There are no adequate and well-controlled studies in nursing mothers. It is not known if milnacipran is excreted in human milk. Studies in animals have shown that milnacipran or its metabolites are excreted in breast milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from milnacipran, a decision should be made whether to discontinue the drug, taking into account the importance of the drug to the mother. Because the safety of Savella in infants is not known, nursing while on Savella is not recommended.

**8.4 Pediatric Use**
Safety and effectiveness of Savella in a fibromyalgia pediatric population below the age of 17 have not been established [*see Box Warning* and *Warnings and Precautions (5.1)*]. The use of Savella is not recommended in pediatric patients.

**8.5 Geriatric Use**
In controlled clinical studies of Savella, 402 patients were 60 years or older, and no overall differences in safety and efficacy were observed between these patients and younger patients. In view of the predominant excretion of unchanged milnacipran via kidneys and the expected decrease in renal function with age renal function should be considered prior to use of Savella in the elderly [*see Dosage and Administration (2.2)*].

SNRIs, SSRIs, and Savella, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event [*see Warnings and Precautions (5.8)*].

**9 DRUG ABUSE AND DEPENDENCE**

**9.1 Controlled Substance**
Milnacipran is not a controlled substance.

**9.2 Abuse**
Milnacipran did not produce behavioral signs indicative of abuse potential in animal or human studies.

**9.3 Dependence**
Milnacipran produces physical dependence, as evidenced by the emergence of withdrawal symptoms following drug discontinuation, similar to other SNRIs and SSRIs. These withdrawal symptoms can be severe. Thus, Savella should be tapered and not abruptly discontinued after extended use. [see *Section 5.7 Discontinuation of Treatment with Savella*].

**10 OVERDOSAGE**
There is limited clinical experience with Savella overdose in humans. In clinical trials, cases of acute ingestions up to 1000 mg, alone or in combination with other drugs, were reported with none being fatal.

In postmarketing experience, fatal outcomes have been reported for acute overdoses primarily involving multiple drugs but also with Savella only. The most common signs and symptoms included increased blood pressure, cardio-respiratory arrest, changes in the level of consciousness (ranging from somnolence to coma), confusional state, dizziness, and increased hepatic enzymes.

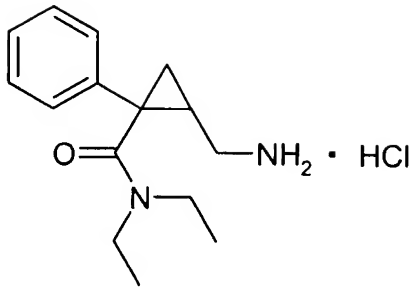
**Management of Overdose**
There is no specific antidote to Savella, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. In case of acute overdose, treatment should consist of those general measures employed in the management of overdose with any drug.

An adequate airway, oxygenation, and ventilation should be assured and cardiac rhythm and vital signs should be monitored. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Because there is no specific antidote for Savella, symptomatic care and treatment with gastric lavage and activated charcoal should be considered as soon as possible for patients who experience a Savella overdose.

Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be beneficial.

In managing overdose, the possibility of multiple drug involvement should be considered. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

**11 DESCRIPTION**
Milnacipran hydrochloride is a selective norepinephrine and serotonin reuptake inhibitor; it inhibits norepinephrine uptake with greater potency than serotonin. It is a racemic mixture with the chemical name: (±)-[1R(S),2S(R)]-2-(aminomethyl)-N,N-diethyl-1-phenylcyclopropanecarboxamide hydrochloride. The structural formula is:




Milnacipran hydrochloride is a white to off-white crystalline powder with a melting point of 179°C. It is freely soluble in water, methanol, ethanol, chloroform, and methylene chloride and sparingly soluble in diethyl ether. It has an empirical formula of C15H23ClN2O and a molecular weight of 282.8 g/mol.

Savella is available for oral administration as film-coated tablets containing 12.5 mg, 25 mg, 50 mg, and 100 mg milnacipran hydrochloride. Each tablet also contains dibasic calcium phosphate, povidone, carboxymethylcellulose calcium, colloidal silicon dioxide, magnesium stearate, and talc as inactive ingredients. Additionally, the following inactive ingredients are also present as components of the film coat:
12.5 mg:
FD&C Red #40 Aluminum Lake dye, hypromellose, polyethylene glycol, titanium dioxide
25 mg:
Hypromellose, polyethylene glycol, titanium dioxide
50 mg:
FD&C Blue #1, Blue #2, and Yellow #5 Aluminum Lake dyes; hypromellose; polyethylene glycol; titanium dioxide
100 mg:
FD&C Blue #1 Aluminum Lake dye, hypromellose, polyethylene glycol, titanium dioxide

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The exact mechanism of the central pain inhibitory action of milnacipran and its ability to improve the symptoms of fibromyalgia in humans are unknown. Preclinical studies have shown that milnacipran is a potent inhibitor of neuronal norepinephrine and serotonin reuptake; milnacipran inhibits norepinephrine uptake with approximately 3-fold higher potency in vitro than serotonin without directly affecting the uptake of dopamine or other neurotransmitters. Milnacipran has no significant affinity for serotonergic (5-HT1-7), α- and β-adrenergic, muscarinic (M1-5), histamine (H1-4), dopamine (D1-5), opiate, benzodiazepine, and γ-aminobutyric acid (GABA) receptors in vitro. Pharmacologic activity at these receptors is hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. Milnacipran has no significant affinity for Ca++, K+, Na+ and Cl– channels and does not inhibit the activity of human monoamine oxidases (MAO-A and MAO-B) or acetylcholinesterase.

### 12.2 Pharmacodynamics

*Cardiovascular Electrophysiology*—The effect of Savella on the QTcF interval was measured in a double-blind placebo- and positive-controlled parallel study in 88 healthy subjects using 600 mg/day Savella (3 to 6 times the recommended therapeutic dose for fibromyalgia). After baseline and placebo adjustment, the maximum mean QTcF change was 8 ms (2-sided 90% CI, 3 - 12 ms). This increase is not considered to be clinically significant.

**12.3 Pharmacokinetics**

Milnacipran is well absorbed after oral administration with an absolute bioavailability of approximately 85% to 90%. The exposure to milnacipran increased proportionally within the therapeutic dose range. It is excreted predominantly unchanged in urine (55%) and has a terminal elimination half-life of about 6 to 8 hours. Steady-state levels are reached within 36 to 48 hours and can be predicted from single-dose data. The active enantiomer, *d*-milnacipran, has a longer elimination half-life (8-10 hours) than the *l*-enantiomer (4-6 hours). There is no interconversion between the enantiomers.

Absorption and Distribution

Savella is absorbed following oral administration with maximum concentrations (Cmax) reached within 2 to 4 hours post dose. Absorption of Savella is not affected by food. The absolute bioavailability is approximately 85% to 90%. The mean volume of distribution of milnacipran following a single intravenous dose to healthy subjects is approximately 400 L.
Plasma protein binding is 13%.

Metabolism and Elimination

Milnacipran and its metabolites are eliminated primarily by renal excretion. Following oral administration of $^{14}$C-milnacipran hydrochloride, approximately 55% of the dose was excreted in urine as unchanged milnacipran (24% as *l*-milnacipran and 31% as *d*-milnacipran). The *l*-milnacipran carbamoyl-O-glucuronide was the major metabolite excreted in urine and accounted for approximately 17% of the dose; approximately 2% of the dose was excreted in urine as *d*-milnacipran carbamoyl-O-glucuronide. Approximately 8% of the dose was excreted in urine as the N-desethyl milnacipran metabolite.

**12.4 Pharmacokinetics in Special Populations**

*Renal Impairment*—Milnacipran pharmacokinetics were evaluated following single oral administration of 50 mg Savella to subjects with mild (creatinine clearance [CLcr] 50-80 mL/min), moderate (CLcr 30-49 mL/min), and severe (CLcr 5-29 mL/min) renal impairment and to healthy subjects (CLcr > 80 mL/min). The mean AUC0-∞ increased by 16%, 52%, and 199%, and terminal elimination half-life increased by 38%, 41%, and 122% in subjects with mild, moderate, and severe renal impairment, respectively, compared with healthy subjects.

No dosage adjustment is necessary for patients with mild renal impairment. Caution should be exercised in patients with moderate renal impairment. Dose adjustment is necessary in severe renal impairment patients. [*see Dosage and Administration (2.2)*].

*Hepatic Impairment*—Milnacipran pharmacokinetics were evaluated following single oral administration of 50 mg Savella to subjects with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment and to healthy subjects. AUC0-∞ and T½ were similar in healthy subjects and subjects with mild and moderate hepatic impairment. However, subjects with severe hepatic impairment had a 31% higher AUC0-∞ and a 55% higher T½ than healthy subjects. Caution should be exercised in patients with severe hepatic impairment.

*Elderly*—Cmax and AUC parameters of milnacipran were about 30% higher in elderly (> 65 years) subjects compared with young subjects due to age-related decreases in renal function. No dosage adjustment is necessary based on age unless renal function is severely impaired [*see Dosage and Administration (2.2)*].

*Gender*—Cmax and AUC parameters of milnacipran were about 20% higher in female subjects compared with male subjects. Dosage adjustment based on gender is not necessary.

*Drug-Drug Interactions*

*In Vitro Studies*
In general, milnacipran, at concentrations that were at least 25 times those attained in clinical trials, did not inhibit human CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 or induce human CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5 enzyme systems, indicating a low potential of interactions with drugs metabolized by these enzymes.

In vitro studies have shown that the biotransformation rate of milnacipran by human hepatic microsomes and hepatocytes was low. A low biotransformation was also observed following incubation of milnacipran with cDNA-expressed human CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 isozymes.

*In Vivo Studies*
The drug interaction studies described in this section were conducted in healthy adult subjects.

Carbamazepine—There were no clinically significant changes in the pharmacokinetics of milnacipran following coadministration of Savella (100 mg/day) and carbamazepine (200 mg twice a day). No changes were observed in the pharmacokinetics of carbamazepine or its epoxide metabolite due to coadministration with Savella.

Clomipramine—Switch from clomipramine (75 mg once a day) to milnacipran (100 mg/day) without a washout period did not lead to clinically significant changes in the pharmacokinetics of milnacipran. Because an increase in adverse events (eg, euphoria and postural hypotension) was observed after switching from clomipramine to milnacipran, monitoring of patients during treatment switch is recommended.

Digoxin—There was no pharmacokinetic interaction between Savella (200 mg/day) and digoxin (0.2 mg/day Lanoxicaps) following multiple-dose administration to healthy subjects.

Fluoxetine—Switch from fluoxetine (20 mg once a day), a strong inhibitor of CYP2D6 and a moderate inhibitor of CYP2C19, to milnacipran (100 mg/day) without a washout period did not affect the pharmacokinetics of milnacipran.

Lithium—Multiple doses of Savella (100 mg/day) did not affect the pharmacokinetics of lithium.

Lorazepam—There was no pharmacokinetic interaction between a single dose of Savella (50 mg) and lorazepam (1.5 mg).

Warfarin—Steady-state milnacipran (200 mg/day) did not affect the pharmacokinetics of R-warfarin and S-warfarin or the pharmacodynamics (as assessed by measurement of prothrombin INR) of a single dose of 25 mg warfarin. The pharmacokinetics of Savella were not altered by warfarin.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis
Dietary administration of milnacipran to rats at doses of 50 mg/kg/day (2 times the MRHD on a mg/m$^2$ basis) for 2 years caused a statistically significant increase in the incidence of thyroid C-cell adenomas and combined adenomas and carcinomas in males. A carcinogenicity study was conducted in Tg.rasH2 mice for 6 months at oral gavage doses of up to 125 mg/kg/day.

Milnacipran did not induce tumors in Tg.rasH2 mice at any dose tested.

Mutagenesis
Milnacipran was not mutagenic in the in vitro bacterial reverse mutation assay (Ames test) or in the L5178Y TK +/- mouse lymphoma forward mutation assay. Milnacipran was also not clastogenic in an in vitro chromosomal aberration test in human lymphocytes or in the in vivo mouse micronucleus assay.

Impairment of Fertility
Although administration of milnacipran to male and female rats had no statistically significant effect on mating or fertility at doses up to 80 mg/kg/day (4 times the MRHD on an mg/m$^2$ basis) there was an apparent dose-related decrease in the fertility index at clinically relevant doses based on body surface area.

**13.2 Animal Toxicology and Pharmacology**
**Hepatic Effects**
Chronic administration (2-years) of milnacipran to rats at 15 mg/kg (0.6 times the MRHD on an mg/m$^2$ basis) and higher doses showed increased incidences of centrilobular vacuolation of the liver in male rats and eosinophilic foci in male and female rats in the absence of any change in hepatic enzymes. The clinical significance of the finding is not known. Chronic (1-year) administration in the primate at doses up to 25 mg/kg (2 times the MRHD on a mg/m$^2$ basis) did not demonstrate similar evidence of hepatic changes.

**Ocular Effects**
Chronic (2-years) administration of milnacipran to rats at 15 mg/kg (0.6 times the MRHD on a mg/m$^2$ basis) and higher doses showed increased incidence of keratitis of the eye. One year studies in the rat and primate did not show this response.

**14 CLINICAL STUDIES**

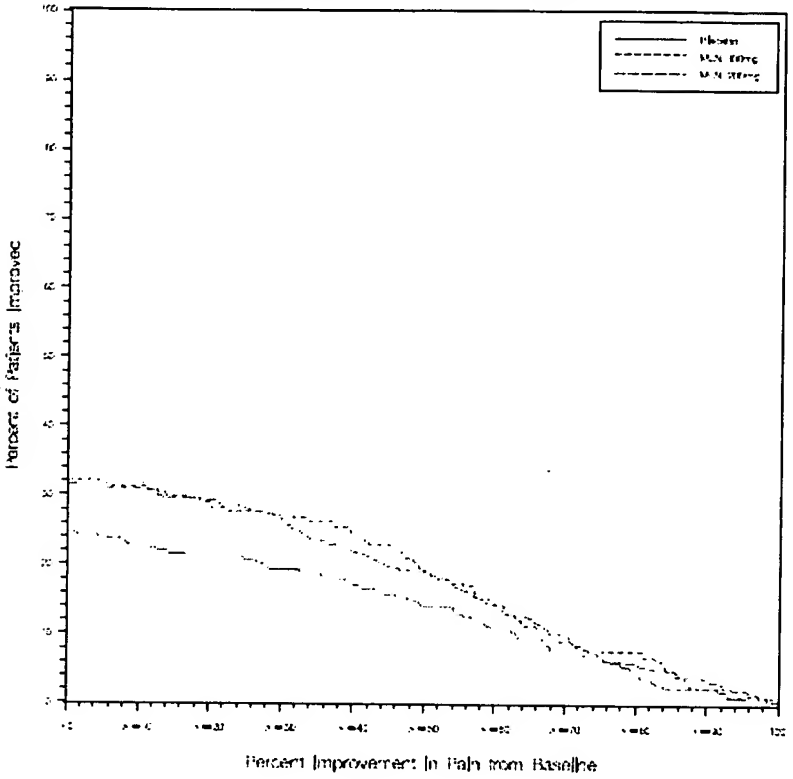
**Management of Fibromyalgia**
The efficacy of Savella for the management of fibromyalgia was established in two double-blind, placebo-controlled, multicenter studies in adult patients (18-74 years of age). Enrolled patients met the American College of Rheumatology (ACR) criteria for fibromyalgia (a history of widespread pain for 3 months and pain present at 11 or more of the 18 specific tender point sites). Approximately 35% of patients had a history of depression. Study 1 was six months in duration and Study 2 was three months in duration.

A larger proportion of patients treated with Savella than with placebo experienced a simultaneous reduction in pain from baseline of at least 30% (VAS) and also rated themselves as much improved or very much improved based on the patient global assessment (PGIC). In addition, a larger proportion of patients treated with Savella met the criteria for treatment response, as measured by the composite endpoint that concurrently evaluated improvement in pain (VAS), physical function (SF-36 PCS), and patient global assessment (PGIC), in fibromyalgia as compared to placebo.

Study 1: This 6-month study compared total daily doses of Savella 100 mg and 200 mg to placebo. Patients were enrolled with a minimum mean baseline pain score of ≥ 50 mm on a 100 mm visual analog scale (VAS) ranging from 0 ("no pain") to 100 ("worst possible pain"). The mean baseline pain score in this trial was 69. The efficacy results for Study 1 are summarized in Figure 1.

Figure 1 shows the proportion of patients achieving various degrees of improvement in pain from baseline to the 3-month time point and who concurrently rated themselves globally improved (PGIC score of 1 or 2). Patients who did not complete the 3-month assessment were assigned 0% improvement. More patients in the Savella treatment arms experienced at least a 30% reduction in pain from baseline (VAS) and considered themselves globally improved (PGIC) than did patients in the placebo arm. Treatment with Savella 200 mg/day did not confer greater benefit than treatment with Savella 100 mg/day.

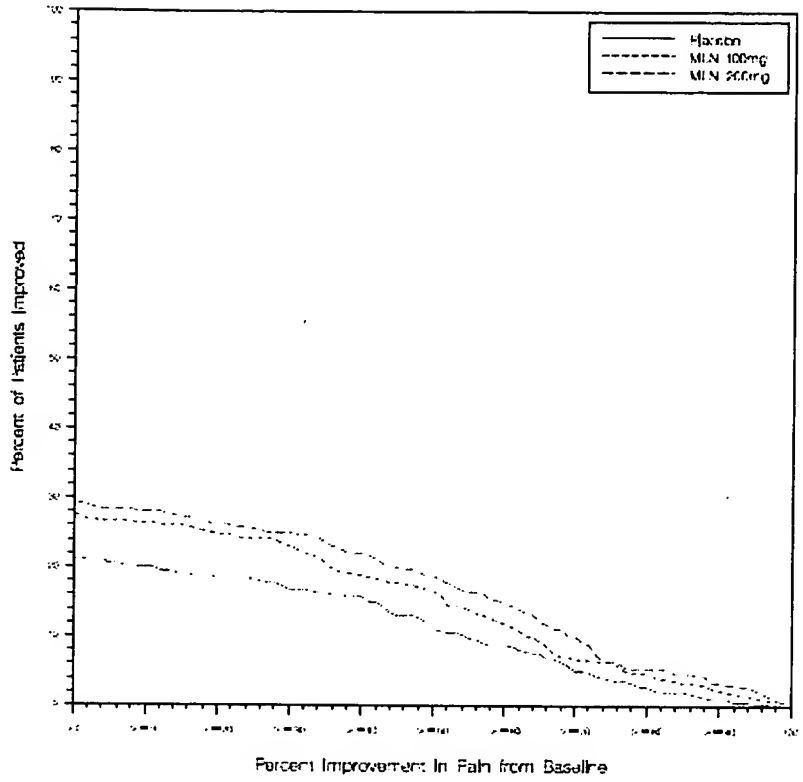
**Figure 1:** Patients Achieving Various Levels of Pain Relief with Concurrent Ratings of Being Much or Very Much Improved on the PGIC — Study 1



Study 2: This 3-month study compared total daily doses of Savella 100 mg and 200 mg to placebo. Patients were enrolled with a minimum mean baseline pain score of ≥ 40 mm on a 100-mm VAS ranging from 0 ("no pain") to 100 ("worst possible pain"). The mean baseline pain score in this trial was 65. The efficacy results for Study 2 are summarized in Figure 2.

Figure 2 shows the proportion of patients achieving various degrees of improvement in pain from baseline to the 3-month time point and who concurrently rated themselves globally improved (PGIC score of 1 or 2). Patients who did not complete the 3-month assessment were assigned 0% improvement. More patients in the Savella treatment arms experienced at least a 30% reduction in pain from baseline (VAS) and considered themselves globally improved (PGIC) than did patients in the placebo arm. Treatment with Savella 200 mg/day did not confer greater benefit than treatment with Savella 100 mg/day.

**Figure 2:** Patients Achieving Various Levels of Pain Relief with Concurrent Ratings of Being Much or Very Much Improved on the PGIC — Study 2




In both studies, some patients who rated themselves as globally "much" or "very much" improved experienced a decrease in pain as early as week 1 of treatment with a stable dose of Savella that persisted throughout these studies.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

***12.5-mg tablets:***
Pink, round, film-coated tablets, debossed with "F" on one side and "L" on the reverse
Bottles of 60: NDC 0456-1512-60

***25-mg tablets:***
White, round, film-coated tablets, debossed with "FL" on one side and "25" on the reverse
Bottles of 60: NDC 0456-1525-60
Bottles of 180: NDC 0456-1525-01

***50-mg tablets:***
Green, oval-shaped, film-coated tablets, debossed with "FL" on one side and "50" on the reverse
Bottles of 60: NDC 0456-1550-60
Bottles of 180: NDC 0456-1550-01

***100-mg tablets:***
Blue, oval-shaped film-coated tablets, debossed with "FL" on one side and "100" on the reverse
Bottles of 60: NDC 0456-1510-60
Bottles of 180: NDC 0456-1510-01

***Titration Pack:***
4-Week Titration Pack: NDC 0456-1500-55
Blister package containing 55 tablets: 5 x 12.5-mg tablets, 8 x 25-mg tablets, and 42 x 50 mg tablets.

**Storage**
Store at 25°C.(77°F); excursions permitted between 15°C and 30°C (between 59°F and 86°F) [See USP Controlled Room Temperature].

## 17 PATIENT COUNSELING INFORMATION

See Medication Guide

### 17.1 Information in Medication Guide

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Savella and should counsel them in its appropriate use. A patient Medication Guide is available for Savella. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Savella:

### 17.2 Suicide Risk

Patients and their families and caregivers should be advised that Savella is a selective norepinephrine and serotonin reuptake inhibitor and therefore belongs to the same class of drugs as antidepressants. Patients, their families and their caregivers should be advised that patients with depression may be at increased risk for clinical worsening and/or suicidal ideation if they stop taking anti-depressant medication, change the dose, or start a new medication.

Patients, their families and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania or other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during treatment with Savella or other drugs that inhibit the reuptake of norepinephrine and/or serotonin, and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. [*see Box Warning and Warnings and Precautions (5.1)*].

### 17.3 Serotonin Syndrome

Patients should be cautioned about the risk of serotonin syndrome with concomitant use of Savella and triptans, tramadol, or other serotonergic agents [*see Warnings and Precautions (5.2)*].

### 17.4 Effect on Blood Pressure and Pulse

Patients should be advised that their blood pressure and pulse should be monitored at regular intervals when receiving treatment with Savella [*see Warnings and Precautions (5.3, 5.4)*].

### 17.5 Abnormal Bleeding

Patients should be cautioned about the concomitant use of Savella and NSAIDs, aspirin, or other drugs that affect coagulation, since the combined use of agents that interfere with serotonin reuptake and these agents has been associated with an increased risk of abnormal bleeding [*see Warnings and Precautions (5.9)*].

**17.6 Ability to Drive and Use Machinery**
Savella might diminish mental and physical capacities necessary to perform certain tasks such as operating machinery, including motor vehicles. Patients should be cautioned about operating machinery or driving motor vehicles until they are reasonably certain that Savella treatment does not affect their ability to engage in such activities.

**17.7 Alcohol**
Patients should be advised to avoid consumption of alcohol while taking Savella [*see Warnings and Precautions (5.6, 5.13)*].

**17.8 Discontinuation**
Patients should be advised that withdrawal symptoms can occur when discontinuing treatment with Savella, particularly when discontinuation is abrupt. [*see Warnings and Precautions (5.7)*]

**17.9 Pregnancy**
Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during Savella therapy [*see Use in Specific Populations (8.1)*].

**17.10 Nursing**
Patients should be advised to notify their physician if they are breast-feeding [*see Use in Specific Populations (8.3)*].

**17.11 FDA-Approved Medication Guide**

**MEDICATION GUIDE**
**Savella (Sa-vel-la) Tablets**
**(milnacipran HCl)**

**Antidepressant Medicines, Depression and other serious Mental Illnesses, and Suicidal Thoughts or Actions**

Savella is not used to treat depression, but it acts like medicines that are used to treat depression (antidepressants) and other psychiatric disorders.

Read the Medication Guide that comes with you or your family member's antidepressant medicine. This Medication Guide is only about the risk of suicidal thoughts or actions with antidepressant medicines. **Talk to your or your family member's healthcare provider about:**

- **all risks and benefits of treatment with antidepressant medicines**
- **all treatment choices for depression or other serious mental illness**

**What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?**

1. **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**
2. **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family

history of) bipolar illness (also called manicdepressive illness) or suicidal thoughts or actions.

3. **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**
    - Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
    - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
    - Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

**Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:**

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood
- trouble sleeping (insomnia)

**What else do I need to know about antidepressant medicines?**

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured for:
Forest Pharmaceuticals, Inc.
Manufactured by:
Forest Laboratories, Inc.

Licensed from Pierre Fabre Medicament and Cypress Bioscience, Inc.

**Revised: January 2009**

# EXHIBIT E

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-256

**NDA APPROVAL**

Cypress Bioscience, Inc.
c/o Forest Laboratories, Inc.
Harborside Financial Center
Plaza III, Suite 602
Jersey City, NJ 07311

Attention: Michael K. Olchaskey, PharmD
Director, Regulatory Affairs

Dear Dr. Olchaskey:

Please refer to your new drug application (NDA) dated and received December 18, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Savella (milnacipran HCl) 12.5 mg, 25 mg, 50 mg, and 100 mg Tablets.

We acknowledge receipt of your submissions dated January 18 and 30, February 8, 11, 13, 15, and 28, March 17 and 31, April 10, 17, 22, 28, and 30, May 30, June 2, 9, 10, 11, and 26, July 3, 15, 28, and 30, August 6, 7, 8, 11, 12, 13, 19, 20, 25, 26, and 27, September 2, 5, 16, 17, and 23, and October 8, 9, 10, 14, 15, 16, 17, and 24, 2008, and January 2 and 8, 2009.

This new drug application provides for the use of Savella (milnacipran HCl) Tablets for the management of fibromyalgia.

We have completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

Your application was not referred to an advisory committee because, although Savella is a new molecular entity, it is not the first drug in the class of norepinephrine-serotonin reuptake inhibitors (NSRIs) indicated for the management of fibromyalgia, the clinical study design was acceptable, and the product did not pose unique concerns beyond those applicable to other members of this class.

## REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the

product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 through 12 years for this application because necessary studies are impossible or highly impracticable. The population of pediatric fibromyalgia patients 12 years of age and younger is extremely small.

We are deferring submission of your pediatric study for ages 13 through 17 years for this application until October 2014 because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required under section 505B(a) of the FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. This required study is listed below.

1. Deferred pediatric study under PREA for the management of fibromyalgia in pediatric patients ages 13 through 17

   You will conduct this trial according to the following timetable:

   | | |
   |---|---|
   | Protocol Submission: | July 2009 |
   | Study Start Date: | January 2010 |
   | Final Report Submission: | October 2014 |

Submit the protocol to your IND 63,736 with a cross-reference letter to your NDA 22-256. Submit the final report to your NDA 22-256. Prominently identify the submissions with the following wording in bold, capital letters at the top of the first page of the submission:

**REQUIRED PEDIATRIC ASSESSMENT**

**RISK EVALUATION AND MITIGATION STRATEGIES (REMS) REQUIREMENTS**

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the FDCA to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). This provision took effect on March 25, 2008.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Savella (milnacipran HCl) to ensure that the benefits of the drug outweighs the risks. Savella (milnacipran HCl) is a norepinephrine and serotonin reuptake inhibitor. The known serious risks associated with drugs of this class are serious psychiatric symptoms, including suicidal ideation, particularly in patients with depression. Mood disorders, such as major depression, bipolar disorder, major mood disorder, and anxiety disorders, commonly co-occur in patients with fibromyalgia. The REMS, once approved, will create enforceable obligations.

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Savella (milnacipran HCl) poses a serious and significant public health concern requiring distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Savella (milnacipran HCl). FDA has determined that Savella (milnacipran HCl) is a product that has serious risks of which patients should be made aware because information concerning the risk(s) could affect patients' decisions to use, or continue to use Savella (milnacipran HCl). In addition, patient labeling could help prevent serious adverse effects related to the use of the product. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Savella (milnacipran HCl).

Your proposed REMS, submitted on October 9, 2008, and appended to this letter, is approved. The REMS consists of the Medication Guide included with this letter and the timetable for submission of assessments of the REMS included in your October 9, 2008, submission.

Your assessment of the REMS should include an evaluation of:

a. Patients' understanding of the serious risks of Savella (milnacipran HCl)
b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

If you do not submit electronically, please send five copies of your REMS assessment or proposed REMS modification to your NDA. Prominently identify the amendment containing the REMS assessment or proposed REMS with the following wording in bold, capital letters at the top of the first page of the submission:

**NDA 22-256 REMS ASSESSMENT**
**NDA 22-256 PROPOSED REMS MODIFICATION**

**POSTMARKETING REQUIREMENTS UNDER 505(o)**

Title IX, Subtitle A, Section 901 of FDAAA also amends the FDCA to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that it is necessary to assess for a signal of a serious risk among pregnant female patients and neonates exposed to Savella (milnacipran HCL). We have become aware of adverse pregnancy outcomes in neonates of women taking drugs in the same class as Savella (milnacipran HCL) during pregnancy. Now, with the approval of the fibromyalgia indication, the population of patients taking Savella (milnacipran HCL) will be overwhelmingly females of childbearing potential, and a study is necessary to assess for a signal of serious risk. We have

also determined that it is necessary to identify an unexpected serious risk to the nursing infants of women who are treated with Savella (milnacipran HCl).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of a serious risk of adverse reactions in fetuses exposed to Savella (milnacipran HCl) or to identify an unexpected serious risk to the nursing infants of women who are treated with Savella (milnacipran HCl).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) has not yet been established and is therefore not sufficient to assess the signal of a serious risk or identify an unexpected serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following postmarketing study.

2. Develop and maintain a prospective, observational pregnancy exposure registry study conducted in the United States that compares the pregnancy and fetal outcomes of women exposed to Savella (milnacipran HCl) during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital anomalies, spontaneous abortions, stillbirths, elective terminations, and any serious adverse pregnancy outcomes. These events will be assessed among the enrolled women throughout the pregnancy. The events will also be assessed among infants through at least the first year of life. Annual interim reports will be submitted until FDA has acknowledged that sufficient data have been collected.

   You will conduct this study according to the following timetable:

   | | |
   |---|---|
   | Protocol Submission: | July 2009 |
   | Study Start Date: | January 2010 |
   | Final Report Submission: | Within six months of FDA notification that sufficient data have been collected. |

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk to the nursing infants of women who are treated with Savella (milnacipran HCl).

Based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following clinical trial.

3. A single-dose, pharmacokinetic, open-label, clinical trial in healthy, lactating women. Concentrations of Savella (Milnacipran HCl) will be assessed in maternal plasma and breast mild so as to estimate potential infant exposure.

   | | |
   |---|---|
   | Protocol Submission: | August 2009 |
   | Trial Start Date: | August 2010 |

Final Report Submission: February 2012

Submit the protocols to your IND 63,736 with a cross-reference letter to your NDA 22-256. Submit the final reports to your NDA 22-256.

Use the following designators to prominently label all submissions, including supplements, relating to this postmarketing study requirements as appropriate:

**Required Postmarketing Protocol under 505(o)**
**Required Postmarketing Final Report under 505(o)**
**Required Postmarketing Correspondence under 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii), requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii), provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

## CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your October 16, 2008, submission containing final draft carton and container labels.

## CONTENT OF LABELING

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert, text for the Medication Guide) dated January 8, 2009. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 22-256."

Marketing the product(s) with final printed labeling that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

## PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

## LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

## MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Diana L. Walker, Regulatory Project Manager, at (301) 796-4029.

Sincerely,

*{See appended electronic signature page}*

Curt Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures: REMS dated October 9, 2008
Package insert dated January 8, 2009
Medication Guide dated January 8, 2009
Carton and Immediate Container Labels dated October 16, 2008

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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Curtis Rosebraugh
1/14/2009 02:46:03 PM

# EXHIBIT F

Cypress

November 30, 2001

Lee Simon, M.D.
Director
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (HFD-550)
Office of Drug Evaluation V.
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852-1833

RE: Cypress Biosciences, Inc.
Milnacipran for Fibromyalgia Syndrome
Initial IND Serial No. 000

Dear Dr. Simon:

In accordance with 21 CFR 312, an Investigational New Drug application (IND) for milnacipran for the treatment of pain associated with Fibromyalgia Syndrome (FMS) is herewith submitted by Cypress Biosciences, Inc. This IND includes 13 volumes of information; an original and two copies of the Initial IND are enclosed.

Milnacipran is a very well-characterized small molecule that functions through several mechanisms, including re-uptake inhibition of serotonin and noradrenaline. This agent was discovered and originally developed for treatment of major depressive disorders (MDD) by Pierre-Fabre Medicament (PFM) of Paris, France. Clinical development was initiated in the late 1980s, and a large number of toxicology, pharmacology, mechanism and safety trials were conducted at that time. Through the mid-1990s numerous human clinical trials were conducted, leading to approvals in France and over 20 other countries for MDD beginning in 1997.

The safety and efficacy of milnacipran for treatment of MDD have been extensively documented throughout this process. In addition, milnacipran has been evaluated on a more limited basis for the treatment of anxiety and chronic pain.

Milnacipran has an excellent safety profile, backed by an extensive database consisting of over 400,000 patient-exposures during 4+ years of commercial marketing. Safety has been characterized in male and female adults, ranging in age from 18 to 80+, and in patients with various concomitant illnesses. Relatively few contraindications have been discovered, and those which do exist are well-documented in the Investigator's Brochure.

Milnacipran was selected by Cypress as a lead compound to develop for the treatment of fibromyalgia. Cypress has focused on treatment of the chronic pain aspects of FMS, based on the ample evidence that FMS involves a component of generalized heightened pain sensitivity due to pathological processing of pain input within the central nervous system. We and our advisors believe that this alteration in pain processing is related to central sensitization. Central sensitization states have been seen in other conditions, and centrally acting re-uptake inhibitors have been shown in the literature to be somewhat efficacious in this setting. This literature



Cypress Bioscience, Inc. 4350 Executive Drive Suite 325 San Diego, California 92121 p/ 858.452.2323 f/ 858.452.1222 www.cypressbio.com

support for the efficacy of tricyclic antidepressants is discussed further in this submission, and we explain why we believe milnacipran's pharmacological properties appear to make it an appropriate treatment for this indication.

No agent has yet been approved in the U.S. for a FMS indication, and therefore, there is a lack of well-established precedents for selection of a primary endpoint and measurement methodology in clinical studies in FMS. However, as the FMS features chronic widespread pain as a primary diagnostic feature, Cypress believes improvement in patient pain is the primary factor necessary to demonstrate effectiveness of a therapeutic intervention. To this end, we propose to use change in patient reported global pain as the primary endpoint. The methodology we are planning to implement in the Phase II trial is diverse, but it includes use of a proprietary electronic patient diary system developed by Invivodata, Inc. Use of the patient diary allows pain assessment on a frequent daily basis, and provides what we believe is a more accurate reflection of true clinical status than do periodic clinic visits. The electronic diary will be supplemented by a number of other endpoint measures including the McGill Pain Questionnaire (SF-MPQ), the SF-12, the fibromyalgia impact questionnaire (FIQ), the World Health Organization Quality of Life tool (WHOQOL) and more typical VAS-based pain and global clinical impression measures.

PFM has licensed the U.S. rights for milnacipran to Cypress, and under this agreement, PFM will supply the active pharmaceutical ingredient. While PF also manufactures final drug product in Europe, Cypress has selected Patheon of Toronto, Canada, as the vendor for final drug product manufacture for this clinical trial program. Patheon is implementing the exact same formulation and manufacturing process that has been developed over the years at PF in France.

**A Phase II clinical study entitled "A Phase II, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of Milnacipran for Treatment of Fibromyalgia" is the first clinical study planned under this IND.**

This study is designed to enroll approximately 190 patients who meet the 1990 American College of Rheumatology (ACR) criteria for FMS. This study focuses on efficacy determinations while also incorporating dose-ranging elements. Patients entering this study will be washed out of other CNS active agents prior to randomization. The design of this study is a flexible dosing titration design, where active treatment patients will be titrated to higher doses over time, up to a potential maximum dose of 200 mg daily. After patients reach the maximum dose or demonstrate dose-limiting toxicity, they will continue in an 8-week steady dose observation phase. The efficacy endpoint will be based on electronic diary patient-recorded global pain, comparing the change in weekly pain values from endpoint (Week 8) to baseline. We have elected to focus on improvement in global pain as our primary efficacy measure as chronic widespread pain is the hallmark of the fibromyalgia syndrome, and pain relief is a mandatory objective of therapeutic interventions. This goal is consistent with the treatment objectives outlined at the 2001 ACR symposium on the treatment of chronic arthritis pain, and the upcoming American Pain Society guidelines.

Secondary endpoints measured in this trial will include the McGill pain questionnaire, Fibromyalgia Impact Questionnaire, patient global impression, SF-12, Beck Depression Inventory, a quality of life assessment, and patient-reported weekly pain recall at clinic visits.

A Form FDA 1572 and *curricula vitae* for Dr. Daniel Clauw, of the Georgetown University, are included in Item 6. Additional Forms FDA 1572 will be submitted for additional sites as they are

qualified for the study. In addition, a Request for Waiver of Pediatric Studies is included in Item 10, Appendix A.

Cypress is excited to have licensed milnacipran as the lead compound in our FMS initiative. One of the primary considerations in selecting milnacipran was its well-documented safety profile and its current registration in Europe. It is Cypress' belief that this product can be moved through the clinical trial process to ultimately file an NDA submission for a fibromyalgia syndrome indication. The enclosed Initial IND outlines our thoughts on a Phase II and Phase III clinical program that will be initiated in the near future.

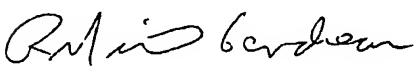
Cypress has had considerable input from rheumatologists, pain specialists and psychiatrists who are thought leaders in the areas of clinical trial design, chronic pain, fibromyalgia, and CNS therapeutics. The designs we have included in these trial submissions represent the consensus that evolved out of these multiple scientific advisory board meetings. Dr. Daniel Clauw, well known in fibromyalgia circles, has agreed to serve as the overall principal investigator for the clinical trial program, as well as serve as the chairman of Cypress' Scientific Advisory Board. Dr. Clauw is available to answer questions or comment on any aspect of the clinical trial designs put forward in this submission.

Milnacipran has an extensive development history and regulatory dossier from its European registration. We have selected the most pertinent studies conducted by PFM and results to include in this IND submission. Where possible, we have provided summaries and global conclusions, and have attempted to avoid overwhelming the FDA reviewers with large numbers of reports from previous studies. We have attached for review what we feel are the most pertinent study reports; but of course, any of the reports listed are available upon request.

We trust the Division will find this Initial IND submission is consistent with current FDA requirements, and look forward to an ongoing dialog with the Division as the clinical trial program progresses.

If you have any questions regarding this Initial IND submission, please contact me at the phone, fax, or address given below.

Sincerely,



R. Michael Gendreau, M.D., Ph.D.
Vice President and Chief Medical Officer
Cypress Bioscience, Inc.
4350 Executive Drive, Suite 325
San Diego, California 92121
Phone: 858-452-2323 x113
FAX: 858-452-1222
mgendreau@CypressBio.com

Enclosures

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

# INVESTIGATIONAL NEW DRUG APPLICATION (IND)

*(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)*

*Form Approved*: OMB No. 0910-0014.
*Expiration Date*: September 30, 2002
*See OMB Statement on Reverse.*

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
Cypress Bioscience, Inc.

2. DATE OF SUBMISSION
30 November 2001

3. ADDRESS *(Number, Street, City, State and Zip Code)*
4350 Executive Drive, Suite 325
San Diego, CA 92121

4. TELEPHONE NUMBER *(Include Area Code)*
(848) 452-2323

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
Milnacipran hydrochloride
(Z-2-Aminomethyl-1-phenyl-N, N-diethylcyclopropane carboxamide hydrochloride)

6. IND NUMBER (If previously assigned)
—

7. INDICATION(S) *(Covered by this submission)*
Fibromyalgia syndrome

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED:
☐ PHASE 1 ☒ PHASE 2 ☐ PHASE 3 ☐ OTHER_____ *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (*21 CFR Part 312*), NEW DRUG OR ANTIBIOTIC APPLICATIONS (*21 CFR Part 314*), DRUG MASTER FILES (*21 CFR 314.420*), AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.

DMF11501

10. ***IND submission should be consecutively numbered. The initial IND should be numbered "Serial Number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.***

SERIAL NUMBER
0 0 0

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*
☒ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND) ☐ RESPONSE TO CLINICAL HOLD

| PROTOCOL AMENDMENT(S): | INFORMATION AMENDMENT(S): | IND SAFETY REPORT(S): |
|---|---|---|
| ☐ NEW PROTOCOL | ☐ CHEMISTRY/MICROBIOLOGY | ☐ INITIAL WRITTEN REPORT |
| ☐ CHANGE IN PROTOCOL | ☐ PHARMACOLOGY/TOXICOLOGY | ☐ FOLLOW-UP TO A WRITTEN REPORT |
| ☐ NEW INVESTIGATOR | ☐ CLINICAL | |

☐ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☐ GENERAL CORRESPONDENCE

☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED ☐ OTHER_____ *(Specify)*

**CHECK ONLY IF APPLICABLE**

**JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.**

☐ **TREATMENT IND 21 CFR 312.35(b)** ☐ **TREATMENT PROTOCOL 21 CFR 312.35(a)** ☐ **CHARGE REQUEST/NOTIFICATION 21 CFR312.7(d)**

**FOR FDA USE ONLY**

| CDR/DBIND/DGD RECEIPT STAMP | DDR RECEIPT STAMP | IND NUMBER ASSIGNED: |
|---|---|---|
| | | DIVISION ASSIGNMENT: 1 0009 |


Created by: PSC Media Arts Branch (301) 443-2454 EF

12. **CONTENTS OF APPLICATION**

This application contains the following items: *(Check all that apply)*

- ! 1. Form FDA 1571 *[21 CFR 312.23 (a)(1)]*
- ☒ 2. Table of Contents *[21 CFR 312.23 (a)(2)]*
- ☒ 3. Introductory statement *[21 CFR 312.23 (a)(3)]*
- ☒ 4. General Investigational plan *[21 CFR 312.23 (a)(3)]*
- ☒ 5. Investigator's brochure *[21 CFR 312.23 (a) 5)]*
- ☒ 6. Protocol(s) *[21 CFR 312.23 (a)(6)]*
  - ☒ a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☒ b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☒ c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☒ d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- ☒ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*
  - ☒ Environmental assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*
- ☒ 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*
- ☒ 9. Previous human experience *[21 CFR 312.23(a)(9)]*
- ☒ 10. Additional information *[21 CFR 312.23(a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☐ YES ☒ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

R. Michael Gendreau, M.D., Ph.D.
Vice President, Development

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

R. Michael Gendreau, M.D., Ph.D.
Vice President, Development

**I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.**

| 16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE | 17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE | |
|---|---|---|
| R. Michael Gendreau, M.D., Ph.D.<br>Vice President, Development | R Michael Gendreau | |
| 18. ADDRESS *(Number, Street, City, State and Zip Code)* | 19. TELEPHONE NUMBER *(Include Area Code)* | 20. DATE |
| 4350 Executive Drive, Suite 325<br>San Diego, CA 92121 | (848) 452-2323 | 29-NOV-2001 |

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CBER (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
5516 Nicholson Lane
Kensington, MD 20895

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please DO NOT RETURN this application to this address.

1 0010

# EXHIBIT G

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 63,736

Cypress Bioscience, Inc.
Attention: R. Michael Gendreau, M.D., Ph.D.
Vice President, Development
4350 Executive Drive, Suite 325
San Diego, CA 92121

Dear Dr. Gendreau:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

| | |
|---|---|
| IND Number Assigned: | 63,736 |
| Sponsor: | Cypress Bioscience, Inc. |
| Name of Drug: | milnacipran hydrochloride capsules |
| Date of Submission: | November 30, 2001 |
| Date of Receipt: | December 3, 2001 |

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, on or before January 2, 2002, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies, we will notify you immediately that (1) clinical studies may not be initiated under this IND ("clinical hold") or that (2) certain restrictions apply to clinical studies under this IND ("partial clinical hold"). In the event of such notification, you must not initiate or you must restrict such studies until you have submitted information to correct the deficiencies, and we have notified you that the information you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports [21 CFR 312.33].

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, to either of the following addresses:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room, N115
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room, N115
9201 Corporate Boulevard
Rockville, Maryland 20850

If you have any questions, please call Ms. Jane A. Dean, Regulatory Health Project Coordinator, at 301-827-2090.

Sincerely,

*{See appended electronic signature page}*

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

---

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

---

/s/

---

Lori Gorski
12/7/01 09:59:08 AM
Lori Gorski has signed for Carmen DeBellas

# EXHIBIT H

**FOREST LABORATORIES, INC.**
**Harborside Financial Center**
**Plaza Three, Suite 602**
**Jersey City, New Jersey 07311**

**Direct Line: (201) 386-2142**
**Fax: (201) 524-9711**

December 18, 2007

Bob Rappaport, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia and Rheumatology Products
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

**NDA:** **22-256 - Milnacipran HCl Tablets**
**Re:** **Original New Drug Application for Fibromyalgia Syndrome (FMS)**
**Request for Priority Review**

Dear Dr. Rappaport:

Forest Laboratories, Inc., on behalf of Cypress Bioscience, Inc. hereby submits an original New Drug Application in the eCTD format for milnacipran hydrochloride tablets, 12.5 mg, 25 mg, 50 mg, and 100 mg, pursuant to the requirements of section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, 21 CFR 314 and supporting Food and Drug Administration guidelines.

Milnacipran is being jointly developed by Cypress Bioscience, Inc. and Forest Laboratories, Inc., in the US, for the treatment of fibromyalgia syndrome (FMS).

Milnacipran hydrochloride, a *cis*-(dl) racemate (Z form) composed of two (*d*- and *l*-) enantiomers is a selective norepinephrine and serotonin reuptake inhibitor (NSRI) with preferential inhibition of norepinepherine reuptake over serotonin reuptake.

Milnacipran was originally discovered by Pierre Fabre Medicament of Cedex, France. In 1997, milnacipran was approved in France for use in patients with major depressive disorder (MDD). As of July 2007, milnacipran has received market approval in 52 countries for major depressive disorder and has more than 20 million patient-months of exposure. Milnacipran is not currently approved in the US for any indication and it has not been submitted for FMS in any country in the world.

Efficacy of milnacipran for fibromyalgia syndrome was evaluated in two pivotal, 3-month, randomized, double-blind, placebo-controlled, multi-center, Phase III clinical studies, conducted in patients with a diagnosis of primary fibromyalgia (Studies MLN-MD-02 and FMS031). Results from these studies show that milnacipran produces statistically significant, clinically meaningful therapeutic benefit and improvement in pain relief, physical function, and global clinical status. In addition to these pivotal studies, two long-term double-blind, randomized, dose-controlled extension studies (Studies MLN-MD-04 and FMS034) provide data supporting the durability of treatment. Results from a placebo-controlled Phase II study (Study FMS021) provide supportive efficacy data. These five studies, along with the results of analyses of the pooled data from the two double-blind placebo-controlled pivotal studies comprise the summary of clinical efficacy.

The safety database consists of 2596 patients exposed to milnacipran: 1824 patients with FMS (one phase II and four phase III studies) and 772 patients with non-FMS disorders (five double-blind, placebo-controlled phase III studies). There were a total of 354 patients treated with milnacipran for at least 1 year in the four double blind FMS studies, of whom 209 were treated at the highest dosage (200 mg/day). In addition there is historical safety data from Pierre Fabre's Marketing Authorization Application (MAA) in MDD conducted prior to 1996; eight pharmacokinetic studies in healthy volunteers; nine post marketing experience studies (after the approval of milnacipran in Europe); and spontaneous-event reports from more than 20 million patient-months of exposure.

## REGULATORY HISTORY

The sponsor has worked in close collaboration with FDA since 2001 and throughout the clinical development of milnacipran for the treatment of FMS. In 2003, Cypress Bioscience, Inc., submitted a special protocol assessment (SPA) to the IND for the design of Study FMS031 with the (former) Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products. Study FMS031 and the entire Phase III program was developed in accordance with the agreements specified in the final SPA.

At a follow-up Type C meeting in June 2006, with the recently merged Division of Anesthesia, Analgesia and Rheumatology Products, the Division informed the sponsor that the requirements for submission had been modified: 6-month data were no longer required for evidence of efficacy, two replicate 3-month pivotal studies would be acceptable for registration, and that the ongoing (6-month) study (Study MLN-MD-02) could be truncated to 3 months for analysis.

In a pre-NDA meeting conducted in March, 2007, the Division confirmed that the two indications discussed in the SPA remained valid: treatment of fibromyalgia syndrome, and treatment of fibromyalgia pain; confirmed that a study length of 3 months is adequate; that baseline observation carried forward (BOCF) is an acceptable and preferred method of imputation, and that the SF-36 Physical Component Summary (PCS) is a valid and acceptable measure of physical function in fibromyalgia. In that same correspondence, the Division agreed that to support the fibromyalgia syndrome and pain indications, the sponsor would submit the results of Study MLN-MD-02, the results of Study FMS031 based upon the pre-specified statistical analysis plan (SAP), the results of Study FMS031 using the analysis methods prospectively specified for Study MLN-MD-02, an integrated (pooled) efficacy analysis of Studies MLN-MD-02 and FMS031 using the analysis method agreed with the Division (Uniform Program Analysis [UPA]) and population (Intent to Treat- [ITT]) specified for Study MLN-MD-02.

Based on the results presented in this submission, the sponsor believes it has satisfied the requirements set forth by the Division for a new claim: treatment of fibromyalgia syndrome. This claim is based on achieving simultaneous and clinically significant improvement in all three major domains of the fibromyalgia syndrome: pain, global and physical function.

## REQUEST FOR PRIORITY REVIEW

The sponsor formally requests a priority review for milnacipran for the treatment of fibromyalgia syndrome. The clinical program presented in this NDA indicates that milnacipran, if approved, has the potential to provide a safe and effective therapy for the treatment of fibromyalgia syndrome with a significantly different and potentially beneficial profile as compared to the currently approved product. Therefore, the Sponsor believes that this NDA meets all the PDUFA criteria for a priority review:

1. FIBROMYALGIA SYNDROME IS A COMMON CONDITION AFFECTING MULTIPLE PHYSICAL AND MENTAL DOMAINS. Fibromyalgia syndrome is a highly prevalent condition affecting 2 to 4 percent of the population according to the American College of Rheumatology (ACR). People with fibromyalgia syndrome have typically turned to pain medicines (including opioids), antidepressants, muscle relaxants, and sleep medicines for relief of their symptoms. Fibromyalgia patients typically have symptoms that extend beyond pain to include numerous other domains including lack of energy/fatigue, impaired sleep, problems with attention or concentration, stiffness, disorganized thinking, difficulty moving, walking or exercising, sluggishness and exhaustion- all of which are symptoms of concern to over 80% of fibromyalgia patients, and which contribute to the multidimensional aspects of fibromyalgia as a syndrome.

2. THERE IS NO THERAPY LABELED FOR THE TREATMENT OF FIBROMYALGIA SYNDROME. Pregabalin recently was approved for the management of Fibromyalgia. However, at this time there is no FDA-approved treatment for Fibromyalgia Syndrome, which includes the improving physical functioning as well as the pain and global impairment of fibromyalgia.

3. MILNACIPRAN IS AN EFFECTIVE TREATMENT FOR FIBROMYALGIA SYNDROME. The large clinical program conducted by the Sponsor indicates that milnacipran, if approved, will provide an effective treatment in Fibromyalgia Syndrome, a condition for which there is no satisfactory alternative therapy. The unique pharmacology profile of milnacipran is well-suited to address the variety of symptoms of the Fibromyalgia Syndrome in addition to pain. Indeed, milnacipran is the first compound to demonstrate efficacy in the Fibromyalgia Syndrome using a responder analysis with composite endpoints specifically developed to assess effectiveness in this condition.

4. MILNACIPRAN IS A SAFE TREATMENT FOR FIBROMYALGIA SYNDROME. A safety database in over 2500 patients, with over 354 patients treated for at least one year, demonstrated that Milnacipran's safety profile is extremely favorable. Adverse events observed in the clinical program are predictable, reversible, clinically manageable and, mostly, mild to moderate in severity. Ten years of post-marketing experience outside the United States in major depression reinforces these safety conclusions.

5. MILNACIPRAN WILL PROVIDE AN ALTERNATIVE TO THE CURRENTLY APPROVED PRODUCT. By providing a mechanism of action different from pregabalin, milnacipran will also provide a different and alternative product for treating patients with Fibromyalgia. This will provide patients with an additional safe and effective alternative if they do not respond or do not tolerate pregabalin. As both pregabalin and milnacipran appear to have beneficial effects in subsets of the fibromyalgia population, it is likely that there will be substantial numbers of patients who are intolerant or unresponsive to any given treatment modality.

In summary, this NDA meets the criteria for a priority review as described in the Manual of Policies and Procedures of the Food and Drug Administration and goals identified in the letters described in section 101(c) of the Food and Drug Administration Amendments Act of 2007, by showing that milnacipran, if approved, has the potential to provide a safe and effective therapy in the treatment of Fibromyalgia

Syndrome, an indication for which currently there is no product specifically approved. In addition, milnacipran provides an alternative therapy with a different mechanism of action to the only currently approved product.

Our NDA submission represents more than 6 years of close collaboration with FDA to commercialize a safe and effective treatment for American patients who suffer from fibromyalgia syndrome

In accordance with Federal Register notice of October 12, 2007, a wire transfer in the amount of $1,178,000 was submitted on November 28, 2007 as payment of the new drug application user fee for human drug application with clinical data.

This application is formatted as required in Title 21 section 3.14.50 of the Code of Federal Regulations and is being submitted in eCTD format in accordance with the "Final Guidance for Industry: Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications". The electronic media consists of 1 copy of the Digital Linear Tape (DLT) created using Backup Utility for Windows (Microsoft and VERITAS Software Corporation) and is approximately 13.5 gigabytes.

This electronic submission has been scanned using McAfee VirusScan Enterprise 8.0.0 Scan Engine 5100 with Virus Definitions 4939 as of January 15, 2007 and is free from computer viruses.

If there are any questions related to this submission, please contact me at (201) 386-2142 or in my absence Sejal A. Parikh, PharmD at (201) 386-2123.

Sincerely,

Michael K. Olchaskey, PharmD
Director, Regulatory Affairs
*michael.olchaskey@frx.com*

# EXHIBIT I

| Chronology of Regulatory Review of Savella™ | |
|---|---|
| **Date** | **Description** |
| February 1984 | PK Studies Initiated (M002 - conducted by Pierre Fabre Medicament outside the U.S.) |
| **November 30, 2001** | **Cypress Bioscience, Inc. (Cypress) submitted Initial IND** |
| December 3, 2001 | FDA Receipt of IND submission |
| **January 2, 2002** | **IND went into effect** |
| March 20, 2002 | Clinical Studies Initiated (FMS021 - First patient first visit) |
| February 26, 2003 | IND Annual Report submitted to FDA |
| March 3, 2003 | Briefing package for Type B End of Phase II Meeting submitted to FDA |
| April 8, 2003 | Meeting with FDA and Cypress (End of Phase II Meeting) |
| May 5, 2003 | FDA issued Official Meeting Minutes for End of Phase II Meeting |
| June 5, 2003 | Briefing package for Type C General Guidance Meeting submitted to FDA |
| July 18, 2003 | Briefing package for the Special Protocol Assessment (SPA) submitted to FDA |
| July 25, 2003 | Meeting with FDA and Cypress - Development Program (Type C General Guidance Meeting) |
| July 31, 2003 | Supplement to SPA submitted to FDA based on comments from FDA at Type C Meeting |
| September 12, 2003 | Comments received from FDA on review of SPA and sponsor's questions |
| September 29, 2003 | Briefing package for Type A meeting to follow up on SPA submitted to FDA |
| October 14, 2003 | Meeting with FDA and Cypress - Development Program (Type A Post SPA Review Meeting) |
| **October 21, 2003** | **Pivotal Clinical Studies initiated (FMS031 - First patient first visit)** |
| October 24, 2003 | FDA issued Official Meeting Minutes for Type A meeting of October 14, 2003 |
| November 6, 2003 | Response to official meeting minutes for Type A meeting of October 14, 2003 |
| November 7, 2003 | Chemistry, Manufacturing, and Controls (CMC) Information amendment submitted to FDA |
| November 7, 2003 | Information amendment (containing pharmacology/toxicology reports) submitted to FDA |
| February 24, 2004 | Transfer of obligations to a Contract Research Organization (CRO) submitted to FDA |
| February 26, 2004 | IND Annual Report submitted to FDA |

| Chronology of Regulatory Review of Savella™ | |
|---|---|
| **Date** | **Description** |
| March 23, 2004 | Request for feedback on draft Statistical Analysis Plan (SAP) for study FMS031, and by extension for study MLN-MD-02, submitted to FDA |
| April 26, 2004 | Information amendment (containing toxicology reports) submitted to FDA |
| May 7, 2004 | CMC Information amendment submitted to FDA |
| June 7, 2004 | Desk copy of toxicology reports submitted on April 26, 2004, was sent to FDA as requested by the FDA review staff |
| July 21, 2004 | CMC Information amendment submitted to FDA |
| July 29, 2004 | PK Studies Initiated under IND (MLN-PK-05 - First patient first visit) |
| August 13, 2004 | FDA provided comments on SAP for study FMS031 |
| September 13, 2004 | Protocol Amendment: New Protocol (Protocol Number: MLN-PK-02) |
| October 1, 2004 | Designation of Forest Laboratories, Inc. (Forest) as regulatory agent for Cypress submitted to FDA |
| October 12, 2004 | Forest acceptance of regulatory obligations submitted to FDA |
| October 13, 2004 | CMC Information amendment submitted to FDA |
| October 26, 2004 | Response to FDA comments on SAP for study FMS031 submitted to FDA |
| November 12, 2004 | Protocol Amendment: RE: (Change in Protocol; New Investigator) |
| December 22, 2004 | Response to FDA request for information regarding the Patient Electronic Diaries (PED) to be used in the pivotal studies |
| January 26, 2005 | FDA responded to sponsor comments of October 26, 2004 |
| February 10, 2005 | Safety Report: Report#: S05-FRA-00496-01; Follow-up |
| March 3, 2005 | IND Annual Report submitted to FDA |
| March 4, 2005 | SAP for study FMS031 submitted to FDA |
| April 7, 2005 | Briefing package for the Type C Meeting (General Guidance) submitted to FDA |
| May 9, 2005 | Meeting with FDA, Cypress, and Forest - Development Program (Type C General Guidance Meeting) |
| June 7, 2005 | FDA issued official meeting minutes from Type C General Guidance Meeting |
| June 15, 2005 | CMC Information amendment submitted to FDA |
| July 5, 2005 | CMC Information amendment submitted to FDA |
| August 15, 2005 | Notice of Intent to request a SPA Carcinogenicity Study submitted to FDA |

| Chronology of Regulatory Review of Savella™ | |
|---|---|
| **Date** | **Description** |
| August 24, 2005 | Information amendment (containing toxicology reports) submitted to FDA |
| September 13, 2005 | Request for SPA for mouse carcinogenicity study submitted to FDA |
| September 19, 2005 | Transfer of obligations for studies FMS031 and MLN-MD-02 submitted to FDA |
| October 24, 2005 | Response to Carc SPA (Final CAC Report) received from FDA |
| November 22, 2005 | Response to FDA request for rat thyroid SAS data submitted to FDA |
| December 16, 2005 | Safety Report: Report# T05-USA-05517-01; Follow-up |
| January 5, 2006 | Protocol Amendment: RE: New Investigator (Protocol Number: MLN-MD-04 ) |
| February 8, 2006 | Safety Report: Report#: T05-USA-03551-01 |
| March 3, 2006 | IND Annual Report submitted to FDA |
| March 21, 2006 | Briefing package for the Type C (Clinical and Statistical Issues) Meeting submitted to FDA |
| April 12, 2006 | Safety Report: Report#: T06-USA-01238-01; Follow-up |
| May 2, 2006 | Protocol Amendment: RE: New Investigator (Protocol Number: MLN-MD-02, MLN-MD-04 ) |
| June 2, 2006 | Meeting with FDA, Cypress, and Forest - Development Program (Type C Meeting - Clinical and Statistical Issues) |
| June 30, 2006 | FDA issued official meeting minutes from Type C (Clinical and Statistical Issues) |
| July 19, 2006 | Safety Report: Report#: T06-USA-02409-01; Follow-up |
| August 14, 2006 | Request for waiver of in vivo bioequivalence study between milnacipran HCl immediate release capsules and tablets submitted to FDA |
| August 23, 2006 | SAP for MLN-MD-02 and Request for feedback on MLN-MD-02 submitted to FDA |
| September 15, 2006 | CMC Information amendment submitted to FDA |
| October 20, 2006 | Request for Type C Meeting (regarding SAP for study MLN-MD-02) submitted to FDA *[Note: Meeting was not granted by FDA]* |
| November 7, 2006 | Safety Report: Report#: T06-GER-04254-01; Follow-up |
| December 1, 2006 | Request for feedback regarding SAP for study MLN-MD-02 submitted to FDA |
| December 13, 2006 | Biowaver granted by FDA for not needing to conducting an in vivo bioequivalence study between immediate release capsules ad tablets |
| **December 18, 2006** | **Pivotal Clinical Studies completed (MLN-MD-02 - Last patient last visit)** |

| Chronology of Regulatory Review of Savella™ | |
|---|---|
| **Date** | **Description** |
| December 21, 2006 | CMC Information amendment submitted to FDA |
| January 26, 2007 | Response received from FDA on SAP for study MLN-MD-02 |
| February 12, 2007 | Briefing package for Pre-NDA Meeting submitted to FDA |
| March 5, 2007 | IND Annual Report submitted to FDA |
| March 16, 2007 | Pre-NDA Meeting with FDA, Cypress, and Forest |
| April 13, 2007 | FDA issued official meeting minutes from Pre-NDA Meeting |
| May 2, 2007 | Response to official meeting minutes from Pre-NDA Meeting submitted to FDA |
| June 19, 2007 | Proposed Pediatric Study Request submitted to FDA |
| June 27, 2007 | Request for feedback submitted to FDA on provision of supporting safety data in NDA |
| July 2, 2007 | Pre-NDA CMC information package submitted to FDA |
| August 6, 2007 | Potential brand name for review submitted to FDA |
| September 20, 2007 | Response to FDA request for information regarding potential brand name submitted to FDA |
| September 27, 2007 | CMC Information amendment submitted to FDA |
| October 5, 2007 | Safety Report: Report#: T07-USA-03210-01; Follow-up |
| November 28, 2007 | CMC Information Amendment submitted to FDA |
| **December 18, 2007** | **NDA submission and FDA receipt of NDA** |
| January 30, 2008 | Proposed 120-day safety update submitted to FDA |
| February 11, 2008 | Teleconference with FDA, Cypress, and Forest regarding change in Division of Anesthesia, Analgesia, and Rheumatology's view on fibromyalgia indication |
| February 29, 2008 | IND Annual Report submitted to FDA |
| March 21, 2008 | Safety Report: Report#: S07-JPN-03266-01 |
| April 11, 2008 | CMC Information amendment submitted to FDA |
| April 17, 2008 | 120-day Safety update submission to FDA |
| May 9, 2008 | General Correspondence: Subject: Other Delineation of Responsibilities: Studies FMS031 and MLN-MD-02 |
| June 5, 2008 | Protocol Amendment: RE:( New Investigator ) ( Protocol Number: MLN-MD-06 ) |
| July 8, 2008 | Safety Report: Report#: L08-JPN-02284-01; Follow-up |

| Chronology of Regulatory Review of Savella™ | |
|---|---|
| **Date** | **Description** |
| August 21, 2008 | Safety Report: Report#: 100000G509; Follow-up |
| September 9, 2008 | Teleconference with FDA, Cypress, and Forest regarding TQT study and Phase IV Commitments |
| October 18, 2008 | Action Date for NDA |
| November 14, 2008 | CMC Information amendment submitted to FDA |
| **January 14, 2009** | **NDA approval** |

# NDA Submission Log

| Record ID | Submission Date / Correspondence Date | To or From Health Authority | Record Type(s) | Summary |
|---|---|---|---|---|
| NDA 22-256 - 1 | 18-Dec-07 | To | Original Application | Original Application: Study Report Group{ ( Study Report Number: FMS & MLN ); } |
| NDA 22-256 - 2 | 18-Jan-08 | To | Response to FDA | Response to FDA: Choose From:( CMC ); |
| NDA 22-256 - 3 | 30-Jan-08 | To | Safety Update | |
| NDA 22-256 - 4 | 8-Feb-08 | To | Response to FDA | Response to FDA: Choose From:( Clinical; Pharmacology Toxicology ); |
| NDA 22-256 - 5 | 11-Feb-08 | To | Response to FDA | Response to FDA: Choose From:( General(all other) ); General{ Subject: SAS codes for primary analysis; } |
| NDA 22-256 - 6 | 13-Feb-08 | To | General Correspondence | General Correspondence: Subject: Sponsor Minutes from Teleconference with FDA on February 11, 2008 |
| NDA 22-256 - 7 | 15-Feb-08 | To | Response to FDA | Response to FDA: Choose From:( General(all other) ); General{ Subject: Request for Information ; } |
| NDA 22-256 - 8 | 25-Feb-08 | To | Response to FDA | Response to FDA: Choose From:( General(all other) ); General{ Subject: Drug Abuse & Dependence; } |
| NDA 22-256 - 9 | 28-Feb-08 | To | Response to FDA | Response to FDA: Choose From:( General(all other) ); General{ Subject: cGMP inspections, statistical analysis of the stability test data, master (blank) batch record for the master blends; } |
| NDA 22-256 - 10 | 17-Mar-08 | To | Response to FDA | Response to FDA: Choose From:( Clinical; Pharmacology Toxicology ); |
| NDA 22-256 - 11 | 31-Mar-08 | To | Response to FDA | Response to FDA: Choose From:( Clinical ); |
| NDA 22-256 - 12 | 10-Apr-08 | To | Response to FDA | Response to FDA: Choose From:( General(all other) ); General{ Subject: Working sample of three-week patient starter pack; sample of the configuration of the blister card for the ten-count sample box; } |
| NDA 22-256 - 47 | 11-Apr-08 | To | General Correspondence | General Correspondence: Subject: Site Audit Documents - Study FMS031 and Study MLN-MD-02 |
| NDA 22-256 - 13 | 17-Apr-08 | To | Safety Update | |
| NDA 22-256 - 14 | 17-Apr-08 | To | Response to FDA | Response to FDA: Choose From:( General(all other) ); General{ Subject: Datasets for protocol violations in FMS-031 & MLN-MD-02; } |
| NDA 22-256 - 15 | 22-Apr-08 | To | Response to FDA | Response to FDA: Choose From:( Clinical; Pharmacology Toxicology ); |
| NDA 22-256 - 16 | 28-Apr-08 | To | General Correspondence | General Correspondence: Subject: Providing a copy of the documents submitted to DSI |

## NDA Submission Log

| Record ID | Submission Date / Correspondence Date | To or From Health Authority | Record Type(s) | Summary |
|---|---|---|---|---|
| NDA 22-256 - 17 | 30-Apr-08 | To | General Correspondence | General Correspondence: Subject: Revised Package Insert |
| NDA 22-256 - 18 | 30-May-08 | To | Response to FDA | Response to FDA: Choose From:( General(all other) ); General{ Subject: Provide copies of the CoAs for the drug substance batches DAL-003, DAL-006, and CA6/174.; } |
| NDA 22-256 - 19 | 2-Jun-08 | To | Response to FDA | Response to FDA: Choose From:( Clinical; General(all other) ); General{ Subject: Clinical/Statistal Requests; } |
| NDA 22-256 - 20 | 9-Jun-08 | To | Response to FDA | Response to FDA: Choose From:( General(all other) ); General{ Subject: CoAs for drug substance batches; } |
| NDA 22-256 - 22 | 10-Jun-08 | To | Response to FDA | Response to FDA: Choose From:( General(all other) ); General{ Subject: Response Regarding Blood Pressure and Heart Rate; } |
| NDA 22-256 - 21 | 11-Jun-08 | To | Response to FDA | Response to FDA: Choose From:( General(all other) ); General{ Subject: Response to FDA Information Request - F1612; } |
| NDA 22-256 - 24 | 26-Jun-08 | To | Response to FDA | Response to FDA: Choose From:( General(all other) ); General{ Subject: Clinical Pharmacology: Enzyme Induction Study Report; } |
| NDA 22-256 - 23 | 3-Jul-08 | To | General Correspondence | General Correspondence: Subject: Submission of Revised Package Insert |
| NDA 22-256 - 25 | 7-Jul-08 | To | Response to FDA | Response to FDA: Choose From:( General(all other) ); General{ Subject: Blood Pressure and Heart Rate; } |
| NDA 22-256 - 26 | 15-Jul-08 | To | Response to FDA | Response to FDA: Choose From:( General(all other) ); General{ Subject: Stastical Review; } |
| NDA 22-256 - 27 | 28-Jul-08 | To | Response to FDA | Response to FDA: Choose From:( CMC ); |
| NDA 22-256 - 28 | 30-Jul-08 | To | Response to FDA | Response to FDA: Choose From:( CMC ); |
| NDA 22-256 - 29 | 6-Aug-08 | To | Response to FDA | Response to FDA: Choose From:( Clinical ); |
| NDA 22-256 - 30 | 7-Aug-08 | To | Response to FDA | Response to FDA: Choose From:( Clinical ); |
| NDA 22-256 - 31 | 8-Aug-08 | To | Response to FDA | Response to FDA: Choose From:( Clinical ); |
| NDA 22-256 - 32 | 8-Aug-08 | To | Response to FDA | Response to FDA: Choose From:( Clinical ); |
| NDA 22-256 - 62 | 11-Aug-08 | To | Response to FDA | Response to FDA: Choose From:( CMC ); |
| NDA 22-256 - 34 | 12-Aug-08 | To | Response to FDA | Response to FDA: Choose From:( Clinical ); |
| NDA 22-256 - 33 | 13-Aug-08 | To | Response to FDA | Response to FDA: Choose From:( Clinical ); |
| NDA 22-256 - 35 | 13-Aug-08 | To | Response to FDA | Response to FDA: Choose From:( CMC; Packaging ); |

# NDA Submission Log

| Record ID | Submission Date / Correspondence Date | To or From Health Authority | Record Type(s) | Summary |
|---|---|---|---|---|
| NDA 22-256 - 36 | 19-Aug-08 | To | Response to FDA | Response to FDA: Choose From:( Pharmacology Toxicology ); |
| NDA 22-256 - 37 | 20-Aug-08 | To | Response to FDA | Response to FDA: Choose From:( General(all other) ); General{ Subject: Non-Clinical; } |
| NDA 22-256 - 38 | 25-Aug-08 | To | Response to FDA | Response to FDA: Choose From:( Packaging ); |
| NDA 22-256 - 39 | 26-Aug-08 | To | Response to FDA | Response to FDA: Choose From:( Clinical ); |
| NDA 22-256 - 40 | 28-Aug-08 | To | Response to FDA | Response to FDA: Choose From:( General(all other) ); General{ Subject: Pediatric Plan; } |
| NDA 22-256 - 41 | 2-Sep-08 | To | Response to FDA | Response to FDA: Choose From:( CMC ); |
| NDA 22-256 - 42 | 5-Sep-08 | To | Response to FDA | Response to FDA: Choose From:( Medical ); |
| NDA 22-256 - 43 | 11-Sep-08 | To | Response to FDA | Response to FDA: Choose From:( Labeling ); |
| NDA 22-256 - 44 | 16-Sep-08 | To | Response to FDA | Response to FDA: Choose From:( Labeling; General(all other) ); General{ Subject: Response to FDA Request (dated September 3, 2008) â€“ Foreign Labels; } |
| NDA 22-256 - 45 | 17-Sep-08 | To | FDA Meeting | FDA Meeting: Date of Meeting: 09-SEP-2008; Subject: Meeting Minutes; Meeting Type: |
| NDA 22-256 - 46 | 23-Sep-08 | To | General Correspondence | General Correspondence: Subject: PROPOSED PEDIATRIC STUDY REQUEST |
| NDA 22-256 - 48 | 8-Oct-08 | To | Response to FDA | Response to FDA: Choose From:( Labeling ); |
| NDA 22-256 - 49 | 9-Oct-08 | To | Response to FDA | Response to FDA: Choose From:( Advertising; General(all other) ); General{ Subject: Postmarketing Commitments (lactation study and pregnancy registry); } |
| NDA 22-256 - 50 | 9-Oct-08 | To | Response to FDA | Response to FDA: Choose From:( General(all other) ); General{ Subject: Proposed Risk Evaluation and Mitigation Strategy (REMS); } |
| NDA 22-256 - 51 | 10-Oct-08 | To | Response to FDA | Response to FDA: Choose From:( Labeling ); |
| NDA 22-256 - 52 | 14-Oct-08 | To | Response to FDA | Response to FDA: Choose From:( CMC; Labeling ); |
| NDA 22-256 - 53 | 15-Oct-08 | To | Response to FDA | Response to FDA: Choose From:( Labeling; Packaging ); |
| NDA 22-256 - 55 | 15-Oct-08 | To | Response to FDA | Response to FDA: Choose From:( Labeling ); |
| NDA 22-256 - 54 | 16-Oct-08 | To | Response to FDA | Response to FDA: Choose From:( Labeling ); |
| NDA 22-256 - 56 | 16-Oct-08 | To | Response to FDA | Response to FDA: Choose From:( Labeling ); |
| NDA 22-256 - 57 | 17-Oct-08 | To | Response to FDA | Response to FDA: Choose From:( Labeling; Packaging ); |
| NDA 22-256 - 58 | 17-Oct-08 | To | Response to FDA | Response to FDA: Choose From:( General(all other) ); General{ Subject: copy of Package Insert; } |

# NDA Submission Log

| Record ID | Submission Date / Correspondence Date | To or From Health Authority | Record Type(s) | Summary |
|---|---|---|---|---|
| NDA 22-256 - 59 | 24-Oct-08 | To | General Correspondence | General Correspondence: Subject: Follow-up to October 17, 2008 Teleconference |
| NDA 22-256 - 60 | 24-Oct-08 | To | General Correspondence | General Correspondence: Subject: Follow-up to October 17, 2008 Teleconference |
| NDA 22-256 - 61 | 24-Oct-08 | To | General Correspondence | General Correspondence: Subject: Follow-up to October 17, 2008 Teleconference. |
| NDA 22-256 - 63 | 2-Jan-09 | To | General Correspondence | General Correspondence: Subject: Action on pending NDA |
| NDA 22-256 - 64 | 8-Jan-09 | To | Response to FDA | Response to FDA: Choose From:( Packaging ); |
| NDA 22-256 - 66 | 14-Jan-09 | From | Approval Letter | Approval Letter: Method of Contact: Letter; Approved Doc Submission Date: 18-Dec-2007; The Approval Letter is for: Original NDA |
| NDA 22-256 - 69 | 14-Jan-09 | From | General Correspondence | General Correspondence: Method of Contact: Letter; Subject: conduct review of Forest Laboratories. |
| NDA 22-256 - 65 | 16-Jan-09 | To | Supplement | Supplement: Choose From:( Changes Being Effected; Labeling; Packaging ); Study Report Group{ ( Study Report Number: ); } |
| NDA 22-256 - 67 | 27-Jan-09 | To | Amendment | Amendment: Choose From:( CMC ); Study Report Number{ ( Study Report Number: ); } |
| NDA 22-256 - 68 | 28-Jan-09 | To | General Correspondence | General Correspondence: Subject: SPL for Approved NDA 22-256 |
| NDA 22-256 - 70 | 10-Feb-09 | To | General Correspondence | General Correspondence: Subject: Request for Enrollment in MedWatch to Manufacture Program (MMP) |
| NDA 22-256 - 71 | 11-Feb-09 | To | General Correspondence | General Correspondence: Subject: Copy of Request for enrollment in MedWatch to Manufacture Program (MMP) |
| NDA 22-256 - 72 | 11-Feb-09 | To | General Correspondence | General Correspondence: Subject: Copy of Request for Enrollment ia MedWatch-to-Manufacture Program (MMP) |
| NDA 22-256 - 73 | 12-Feb-09 | To | General Correspondence | General Correspondence: Subject: Patent Information |
| NDA 22-256 - 74 | 24-Feb-09 | To | Response to FDA | Response to FDA: Choose From:( CMC ); |
| NDA 22-256 - 75 | 27-Feb-09 | To | General Correspondence | General Correspondence: Subject: Update business address of drug product manufacturing site (Name Change) |

# IND Submission Log

| Record ID | S/N | Date | Record Type(s) | Summary |
|---|---|---|---|---|
| IND 63,736 - 0 | 0 | 30-Nov-01 | Initial IND | Initial IND: Study Report Group{ ( Study Report Number: FMS-021 ); }; ( Investigator's Brochure Date: 30-NOV-2001; IND Activation Date: 30-NOV-2001 ); Protocol Group{ ( Protocol Number: FMS-021 ); } |
| IND 63,736 - 1 | 1 | 14-Jan-02 | Response to FDA | Response to FDA: Choose From:( CMC ); |
| IND 63,736 - 2 | 2 | 4-Feb-03 | General Correspondence | General Correspondence: Subject: Request to Confirm Type B End of Phase 2 Meeting for 08 Apr 2003 |
| IND 63,736 - 3 | 3 | 26-Feb-03 | Annual Report | Annual Report: From: 02-JAN-2002; To: 01-JAN-2003 |
| IND 63,736 - 4 | 4 | 26-Feb-03 | Response to FDA | Response to FDA: Choose From:( Pharmacology Toxicology ); |
| IND 63,736 - 5 | 5 | 4-Mar-03 | Briefing Book | |
| IND 63,736 - 6 | 6 | 5-Jun-03 | Briefing Book | |
| IND 63,736 - 7 | 7 | 12-Jun-03 | Briefing Book | |
| IND 63,736 - 8 | 8 | 18-Jun-03 | General Correspondence | General Correspondence: Subject: Withdrawal of Serial 007 |
| IND 63,736 - 9 | 9 | 18-Jul-03 | Briefing Book | |
| IND 63,736 - 10 | 10 | 31-Jul-03 | General Correspondence | General Correspondence: Subject: Supplement To Special Protocol Assessment Outlines The Steps Taken I Phase III Program Discussed With DSI And DAADOP On 25 JUL 2003 |
| IND 63,736 - 11 | 11 | 16-Sep-03 | FDA Meeting | FDA Meeting: Date of Meeting: 06-OCT-2003; Subject: Meeting Request; Meeting Type: A |
| IND 63,736 - 12 | 12 | 29-Sep-03 | FDA Meeting | FDA Meeting: Date of Meeting: 06-Oct-2003; Subject: Meeting Request; Meeting Type: A |
| IND 63,736 - 13 | 13 | 6-Nov-03 | FDA Meeting | FDA Meeting: Date of Meeting: 06-OCT-2003; Subject: Meeting Request; Meeting Type: A |
| IND 63,736 - 14 | | 7-Nov-03 | Information Amendment | Information Amendment: Choose From:( Pharmacology Toxicology ); Toxicology Report Number{ ( Toxicology Report Number: F2695 & F2696 ); } |
| IND 63,736 - 15 | 15 | 7-Nov-03 | Information Amendment | Information Amendment: Choose From:( CMC ); |
| IND 63,736 - 16 | 16 | 10-Nov-03 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: FMS-031 ); }; |
| IND 63,736 - 17 | 17 | 13-Feb-04 | Protocol Amendment | Protocol Amendment: RE:( New Protocol ); New Protocol{ Version Date: 03-FEB-2004; ( Protocol Number: FMS-031 ); }; |
| IND 63,736 - 18 | 18 | 20-Feb-04 | Information Amendment | Information Amendment: Choose From:( Clinical ); Clinical{ ( Study Report Number: FMS-031; Protocol Number: FMS-031; Date of Clinical Study Report: 20-Feb-2004; Report Type: ); }; |
| IND 63,736 - 19 | 19 | 24-Feb-04 | Information Amendment | Information Amendment: Choose From:( Clinical ); Clinical{ Investigator's Brochure Date: 03-OCT-2003; ( Study Report Number: FMS-031; Protocol Number: FMS-031; Date of Clinical Study Report: 24-FEB-2004; Report Type: ); }; |
| IND 63,736 - 20 | 20 | 24-Feb-04 | Information Amendment | Information Amendment: Choose From:( Clinical ); Clinical{ ( Study Report Number: FMS-031; Protocol Number: FMS-031; Date of Clinical Study Report: 24-FEB-2004; Report Type: ); }; |

# IND Submission Log

| Record ID | S/N | Date | Record Type(s) | Summary |
|---|---|---|---|---|
| IND 63,736 - 21 | 21 | 26-Feb-04 | Annual Report | Annual Report: From: 02-JAN-2003; To: 01-SEP-2004 |
| IND 63,736 - 22 | 22 | 23-Mar-04 | General Correspondence | General Correspondence: Subject: General Correspondence: SAP for Protocol FMS031/Request for FDA Feedback |
| IND 63,736 - 23 | 23 | 24-Mar-04 | Protocol Amendment | Protocol Amendment: RE:( New Protocol ); New Protocol{ Version Date: 24-MAR-2004; ( Protocol Number: FMS-034 ); }; |
| IND 63,736 - 24 | 24 | 29-Mar-04 | General Correspondence | General Correspondence: Subject: Enclosed please find new and updated investigator information for investigators that are participating in the FMS031 protocol entitled, A Phase III Pivotal, Multi-center, Double-Blind, Randomized, Placebo-Controlled Mono-therapy Study of Milnacipran for Treatment of Fibromyalgia. |
| IND 63,736 - 25 | 25 | 26-Apr-04 | Information Amendment | Information Amendment: Choose From:( Pharmacology Toxicology ); Toxicology Report Number{ ( Toxicology Report Number: MLN TX-03000, MLN TX-04000 ); } |
| IND 63,736 - 26 | 26 | 6-May-04 | Protocol Amendment | Protocol Amendment: RE:( Change in Protocol ); Change in Protocal{ Version Date: 30-APR-2004; ( Protocol Number: FMS-034 ); }; |
| IND 63,736 - 27 | 27 | 7-May-04 | Safety Report | Safety Report: Report#{ ( Report#: C-031-2004-07; ; Follow-up#: ); } |
| IND 63,736 - 28 | 28 | 7-May-04 | Information Amendment | Information Amendment: Choose From:( CMC ); |
| IND 63,736 - 29 | 29 | 7-May-04 | Safety Report | Safety Report: Report#{ ( Report#: C-031-2004-07; ; Follow-up#: 01 ); } |
| IND 63,736 - 30 | 30 | 7-Jun-04 | General Correspondence | General Correspondence: Subject: Curriculum Vitae and Form 1572 for Investigators Participating in Protocol FMS-034 |
| IND 63,736 - 31 | 31 | 7-Jun-04 | General Correspondence | General Correspondence: Subject: Desk Copy of the Reproductive Toxicology Section from our previous electronic Pre-Clinical Submission, Serial No. 014 |
| IND 63,736 - 32 | 32 | 21-Jul-04 | Information Amendment | Information Amendment: Choose From:( CMC ); |
| IND 63,736 - 33 | 32 | 21-Jul-04 | Protocol Amendment | Protocol Amendment: RE:( New Investigator; New Protocol ); New Investigator{ ( Protocol Number: MLN-PK-05 ); }; New Protocol{ Version Date: 10-JUN-2004; ( Protocol Number: MLN-PK-05 ); }; |
| IND 63,736 - 34 | 34 | 23-Jul-04 | General Correspondence | General Correspondence: Subject: Addendum to PSUR |
| IND 63,736 - 35 | 35 | 13-Aug-04 | Protocol Amendment | Protocol Amendment: RE:( Change in Protocol; New Investigator ); Change in Protocal{ Version Date: 05-AUG-2004; ( Protocol Number: MLN-PK-01 ); }; New Investigator{ ( Protocol Number: MLN-PK-01 ); }; |
| IND 63,736 - 36 | 36 | 13-Sep-04 | Protocol Amendment | Protocol Amendment: RE:( New Protocol ); New Protocol{ Version Date: 24-AUG-2004; ( Protocol Number: MLN-PK-02 ); }; |
| IND 63,736 - 37 | 37 | 1-Oct-04 | General Correspondence | General Correspondence: Subject: Cypress Bioscience, Inc., sponsor of IND 463,736, Milnacipran HC1, hereby informs the Division that effective Friday, October 1, 2004 Forest Laboratories Inc., located at Harborside Financial Center, Plaza Three, Suite 602, Jersey City, New Jersey 07311, will serve as a regulatory representative with respect to the subject IND. |

# IND Submission Log

| Record ID | S/N | Date | Record Type(s) | Summary |
|---|---|---|---|---|
| IND 63,736 - 38 | 38 | 1-Oct-04 | Protocol Amendment | Protocol Amendment: RE:( Change in Protocol ); Change in Protocal{ Version Date: 21-SEP-2004; ( Protocol Number: MLN-PK-02 ); }; |
| IND 63,736 - 39 | 38 | 12-Oct-04 | General Correspondence | General Correspondence: Subject: Forest confirms acceptance of regulatory obligations with respect to the above mentioned IND as of October 7, 2004. (Note that Serial No. 037 [enclosed] erroneously indicated that the effective date was October 1, 2004.) |
| IND 63,736 - 40 | 39 | 13-Oct-04 | Information Amendment | Information Amendment: Choose From:( CMC ); |
| IND 63,736 - 41 | 40 | 18-Oct-04 | Safety Report | Safety Report: Report#{ ( Report#: T04-FRA-06624-01; ; Follow-up#: ); } |
| IND 63,736 - 42 | 41 | 22-Oct-04 | Protocol Amendment | Protocol Amendment: RE:( Change in Protocol; New Protocol ); Change in Protocal{ Version Date: 03-SEP-2004; ( Protocol Number: MLN-MD-02 ); }; New Protocol{ Version Date: 21-OCT-2004; ( Protocol Number: MLN-MD-02 ); }; |
| IND 63,736 - 43 | 42 | 26-Oct-04 | General Correspondence | General Correspondence: Subject: General Correspondence: Response to comments on Statistical Analysis Plan (SAP) for Study FMS031 |
| IND 63,736 - 44 | 43 | 27-Oct-04 | Safety Report | Safety Report: Report#{ ( Report#: S04-JPN-06860-01 (0); ; Follow-up#: ); } |
| IND 63,736 - 45 | 44 | 12-Nov-04 | Safety Report | Safety Report: Report#{ ( Report#: S04-FRA-07478-01 (0), T04-USA-07351-01 (0); , ; Follow-up#: , ); } |
| IND 63,736 - 46 | 45 | 12-Nov-04 | Protocol Amendment | Protocol Amendment: RE:( Change in Protocol; New Investigator ); Change in Protocal{ Version Date: 27-OCT-2004; ( Protocol Number: MLN-PK-01 ); }; New Investigator{ ( Protocol Number: MLN-PK-01 ); }; |
| IND 63,736 - 47 | 46 | 22-Nov-04 | Safety Report | Safety Report: Report#{ ( Report#: T04-USA-07603-01 (0); ; Follow-up#: ); } |
| IND 63,736 - 48 | 47 | 30-Nov-04 | Safety Report | Safety Report: Report#{ ( Report#: T04-USA-07742-01 (0); ; Follow-up#: ); } |
| IND 63,736 - 49 | 48 | 2-Dec-04 | General Correspondence | General Correspondence: Subject: General Correspondence: Clarification of Serial No. 45 dated November 19, 2004 |
| IND 63,736 - 50 | 49 | 3-Dec-04 | Safety Report | Safety Report: Report#{ ( Report#: T04-USA-07033-01 (0), t04-USA-07603-01 , T04-USA-07742-01 ; , Follow-up, ; Follow-up#: , 1, 1 ); } |
| IND 63,736 - 51 | 50 | 8-Dec-04 | Safety Report | Safety Report: Report#{ ( Report#: T04-USA-07742-01; Follow-up; Follow-up#: 2 ); } |
| IND 63,736 - 52 | 51 | 10-Dec-04 | Safety Report | Safety Report: Report#{ ( Report#: S04-FRA-08037-01, S04-FRA-08037-02; , ; Follow-up#: , ); } |
| IND 63,736 - 53 | 52 | 14-Dec-04 | Safety Report | Safety Report: Report#{ ( Report#: S04-JPN-06165-01; ; Follow-up#: ); } |
| IND 63,736 - 54 | 53 | 15-Dec-04 | Safety Report | Safety Report: Report#{ ( Report#: S04-JPN-08164-01; ; Follow-up#: ); } |
| IND 63,736 - 55 | 54 | 16-Dec-04 | Safety Report | Safety Report: Report#{ ( Report#: T04-USA-07603-01; ; Follow-up#: 2 ); } |
| IND 63,736 - 56 | 55 | 21-Dec-04 | Safety Report | Safety Report: Report#{ ( Report#: S04-JPN-08164-01, S04-FRA-08037-01, T04-USA-07351-01; Follow-up, Follow-up, Follow-up; Follow-up#: 1, 1, 1 ); } |
| IND 63,736 - 57 | 56 | 22-Dec-04 | General Correspondence | General Correspondence: Subject: General Correspondence: Response to inquiry from Dr. James Witter regarding the Patient Klectronic Diary (PED) |
| IND 63,736 - 58 | 57 | 5-Jan-05 | Safety Report | Safety Report: Report#{ ( Report#: S04-JPN-08306-01; ; Follow-up#: ); } |

# IND Submission Log

| Record ID | S/N | Date | Record Type(s) | Summary |
|---|---|---|---|---|
| IND 63,736 - 59 | 58 | 5-Jan-05 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-02 ); }; |
| IND 63,736 - 60 | 59 | 18-Jan-05 | Information Amendment | Information Amendment: Choose From:( Clinical ); Clinical{ Investigator's Brochure Date: 22-DEC-2004; ( Study Report Number: MLN-MD-02; Protocol Number: MLN-MD-02; Date of Clinical Study Report: 18-JAN-2005; Report Type: ); }; |
| IND 63,736 - 61 | 60 | 28-Jan-05 | Safety Report | Safety Report: Report#{ ( Report#: S04-JPN-06860-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 62 | 61 | 10-Feb-05 | Safety Report | Safety Report: Report#{ ( Report#: S05-FRA-00496-01; ; Follow-up#: ); } |
| IND 63,736 - 63 | 62 | 11-Feb-05 | Safety Report | Safety Report: Report#{ ( Report#: t04-fra-06624-01; ; Follow-up#: ); } |
| IND 63,736 - 64 | 63 | 23-Feb-05 | Safety Report | Safety Report: Report#{ ( Report#: S05-FRA-00733-01; ; Follow-up#: ); } |
| IND 63,736 - 65 | 64 | 28-Feb-05 | Safety Report | Safety Report: Report#{ ( Report#: S05-JPN-00744-01; ; Follow-up#: ); } |
| IND 63,736 - 66 | 65 | 3-Mar-05 | Annual Report | Annual Report: From: 02-JAN-2004; To: 01-JAN-2005 |
| IND 63,736 - 67 | 66 | 4-Mar-05 | General Correspondence | General Correspondence: Subject: General Correspondence: Statistical Analysis Plan (SAP) for Study FMS031 |
| IND 63,736 - 68 | 67 | 8-Mar-05 | General Correspondence | General Correspondence: Subject: Request for Type C Meeting |
| IND 63,736 - 69 | 68 | 18-Mar-05 | Safety Report | Safety Report: Report#{ ( Report#: S05-JPN-01065-01; ; Follow-up#: ); } |
| IND 63,736 - 70 | 69 | 29-Mar-05 | Safety Report | Safety Report: Report#{ ( Report#: S05-FRA-01237-01; ; Follow-up#: ); } |
| IND 63,736 - 71 | 70 | 7-Apr-05 | Briefing Book | |
| IND 63,736 - 72 | 71 | 13-Apr-05 | Safety Report | Safety Report: Report#{ ( Report#: S05-FRA-01409-01; ; Follow-up#: ); } |
| IND 63,736 - 73 | 72 | 14-Apr-05 | Protocol Amendment | Protocol Amendment: RE:( Change in Protocol; New Investigator ); Change in Protocal{ Version Date: 28-MAR-2005; ( Protocol Number: MLN-PK-11 ); }; New Investigator{ ( Protocol Number: MLN-PK-11 ); }; |
| IND 63,736 - 74 | 73 | 15-Apr-05 | General Correspondence | General Correspondence: Subject: General Correspondence: REQUEST FOR REVIEW-DRAFT Protocol-MLN-PK-10 |
| IND 63,736 - 75 | 74 | 18-Apr-05 | Safety Report | Safety Report: Report#{ ( Report#: S05-JPN-01065-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 76 | 75 | 19-Apr-05 | Safety Report | Safety Report: Report#{ ( Report#: S05-FRA-01409-01, S05-FRA-01418-01; Follow-up, ; Follow-up#: 1, ); } |
| IND 63,736 - 77 | 76 | 21-Apr-05 | Protocol Amendment | Protocol Amendment: RE:( Change in Protocol ); Change in Protocal{ Version Date: 31-MAR-2005; ( Protocol Number: FMS-031 ); }; |
| IND 63,736 - 78 | 77 | 25-Apr-05 | Safety Report | Safety Report: Report#{ ( Report#: S05-FRA-01418-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 79 | 78 | 26-Apr-05 | Safety Report | Safety Report: Report#{ ( Report#: S05-JPN-01065-01; Follow-up; Follow-up#: 2 ); } |
| IND 63,736 - 80 | 79 | 27-Apr-05 | Safety Report | Safety Report: Report#{ ( Report#: S05-FRA-01498-01; ; Follow-up#: ); } |
| IND 63,736 - 81 | 80 | 28-Apr-05 | Safety Report | Safety Report: Report#{ ( Report#: S05-JPN-01558-01; ; Follow-up#: ); } |

# IND Submission Log

| Record ID | S/N | Date | Record Type(s) | Summary |
|---|---|---|---|---|
| IND 63,736 - 82 | 81 | 2-May-05 | Protocol Amendment, General C | General Correspondence: Subject: Summary of Changes-FMS-031 Protocol Amendment 3 Protocol Amendment: RE:( Change in Protocol ); Change in Protocal{ Version Date: 07-MAR-2005; ( Protocol Number: FMS-031 ); }; |
| IND 63,736 - 83 | 82 | 4-May-05 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-02 ); }; |
| IND 63,736 - 84 | 83 | 4-May-05 | Safety Report | Safety Report: Report#{ ( Report#: S05-FRA-01498-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 85 | 84 | 11-May-05 | General Correspondence | General Correspondence: Subject: General Correspondence: Meeting Minutes from May 9, 2005 Meeting |
| IND 63,736 - 86 | 85 | 17-May-05 | Safety Report | Safety Report: Report#{ ( Report#: S05-JPN-01558-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 87 | 86 | 18-May-05 | Safety Report | Safety Report: Report#{ ( Report#: S05-JPN-01802-01; ; Follow-up#: ); } |
| IND 63,736 - 88 | 87 | 25-May-05 | Protocol Amendment | Protocol Amendment: RE:( New Protocol ); New Protocol{ Version Date: 13-MAY-2005; ( Protocol Number: MLN-PK-10 ); }; |
| IND 63,736 - 89 | 88 | 26-May-05 | Safety Report | Safety Report: Report#{ ( Report#: S05-FRA-01237-01; ; Follow-up#: ); } |
| IND 63,736 - 90 | 89 | 31-May-05 | Safety Report | Safety Report: Report#{ ( Report#: S05-FRA-01498-01; Follow-up; Follow-up#: 2 ); } |
| IND 63,736 - 91 | 90 | 3-Jun-05 | Safety Report | Safety Report: Report#{ ( Report#: S05-JPN-01065-01; Follow-up; Follow-up#: 3 ); } |
| IND 63,736 - 92 | 91 | 7-Jun-05 | Safety Report | Safety Report: Report#{ ( Report#: S05-FRA-01237-01; Follow-up; Follow-up#: 2 ); } |
| IND 63,736 - 93 | 92 | 10-Jun-05 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-02 ); }; |
| IND 63,736 - 94 | 93 | 10-Jun-05 | Safety Report | Safety Report: Report#{ ( Report#: T05-USA-01966-01; ; Follow-up#: ); } |
| IND 63,736 - 96 | 95 | 14-Jun-05 | Safety Report | Safety Report: Report#{ ( Report#: S05-JPN-01065-01; Follow-up; Follow-up#: 4 ); } |
| IND 63,736 - 95 | 94 | 15-Jun-05 | Information Amendment | Information Amendment: Choose From:( CMC ); |
| IND 63,736 - 97 | 96 | 21-Jun-05 | Safety Report | Safety Report: Report#{ ( Report#: T05-USA-01966-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 98 | 97 | 23-Jun-05 | Protocol Amendment | Protocol Amendment: RE:( New Protocol ); New Protocol{ Version Date: 04-MAY-2005; ( Protocol Number: MLN-MD-04 ); }; |
| IND 63,736 - 99 | 98 | 24-Jun-05 | Safety Report | Safety Report: Report#{ ( Report#: T05-USA-02053-01; ; Follow-up#: ); } |
| IND 63,736 - 100 | 99 | 5-Jul-05 | Information Amendment | Information Amendment: Choose From:( CMC ); |
| IND 63,736 - 101 | 100 | 13-Jul-05 | Safety Report | Safety Report: Report#{ ( Report#: S05-JPN-02373-01; ; Follow-up#: ); } |
| IND 63,736 - 102 | 101 | 19-Jul-05 | Safety Report | Safety Report: Report#{ ( Report#: T04-FRA-06624-01; Follow-up; Follow-up#: 2 ); } |
| IND 63,736 - 103 | 102 | 20-Jul-05 | Safety Report | Safety Report: Report#{ ( Report#: S05-BRA-02376-01; ; Follow-up#: ); } |
| IND 63,736 - 104 | 103 | 21-Jul-05 | Safety Report | Safety Report: Report#{ ( Report#: T05-USA-02053-01; Follow-up; Follow-up#: 1 ); } |

# IND Submission Log

| Record ID | S/N | Date | Record Type(s) | Summary |
|---|---|---|---|---|
| IND 63,736 - 105 | 104 | 26-Jul-05 | Information Amendment | Information Amendment: Choose From:( Clinical ); Clinical{ Investigator's Brochure Date: 30-NOV-2001; ( Study Report Number: FMS-031; Protocol Number: FMS-031; Date of Clinical Study Report: 26-JUL-2005; Report Type: ); }; |
| IND 63,736 - 106 | 105 | 3-Aug-05 | Safety Report | Safety Report: Report#{ ( Report#: T05-FRA-02448-01, S05-JPN-02612-01; , ; Follow-up#: , ); } |
| IND 63,736 - 107 | 106 | 5-Aug-05 | Safety Report | Safety Report: Report#{ ( Report#: T04-FRA-06624-01, T05-USA-01966-01; Follow-up, Follow-up; Follow-up#: 3, 2 ); } |
| IND 63,736 - 108 | 107 | 8-Aug-05 | Safety Report | Safety Report: Report#{ ( Report#: S05-FRA-02620-01; ; Follow-up#: ); } |
| IND 63,736 - 109 | 108 | 10-Aug-05 | Protocol Amendment | Protocol Amendment: RE:( Change in Protocol; New Investigator ); Change in Protocal{ Version Date: 06-JUL-2005; ( Protocol Number: MLN-PK-10 ); }; New Investigator{ ( Protocol Number: MLN-PK-10 ); }; |
| IND 63,736 - 110 | 109 | 15-Aug-05 | General Correspondence | General Correspondence: Subject: Notice of Intent to Request a Special Protocol Assessment - Carcinogenicity Study |
| IND 63,736 - 111 | 110 | 22-Aug-05 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-02, MLN-MD-04 ); }; |
| IND 63,736 - 113 | 111 | 23-Aug-05 | Safety Report | Safety Report: Report#{ ( Report#: T04-USA-07742-01; Follow-up; Follow-up#: 3 ); } |
| IND 63,736 - 114 | 112 | 24-Aug-05 | Safety Report | Safety Report: Report#{ ( Report#: S05-JPN-01065-01; Follow-up; Follow-up#: 5 ); } |
| IND 63,736 - 115 | 113 | 24-Aug-05 | Information Amendment | Information Amendment: Choose From:( Pharmacology Toxicology ); Toxicology Report Number{ ( Toxicology Report Number: F2207-0314/101-2004 ); } |
| IND 63,736 - 116 | 114 | 25-Aug-05 | Safety Report, Response to FDA | Response to FDA: Choose From:( General(all other) ); General{ Subject: Response to FDA Inquiry dated May 6, 2005; Note that this case is a spontaneous report, and that this Japanese patient was not enrolled in a study, and as such there is no case report form.; } Safety Report: Report#{ ( Report#: S05-JPN-01065-01; Follow-up; Follow-up#: 5 ); } |
| IND 63,736 - 117 | 115 | 31-Aug-05 | Safety Report | Safety Report: Report#{ ( Report#: T05-USA-01966-01; Follow-up; Follow-up#: 3 ); } |
| IND 63,736 - 118 | 116 | 1-Sep-05 | Safety Report | Safety Report: Report#{ ( Report#: S05-JPN-01065-0l; Follow-up; Follow-up#: 6 ); } |
| IND 63,736 - 119 | 117 | 13-Sep-05 | Protocol Amendment | Protocol Amendment: RE:( Change in Protocol ); Change in Protocal{ Version Date: 07-SEP-2005; ( Protocol Number: MLN-PK-10 ); }; |
| IND 63,736 - 120 | 118 | 13-Sep-05 | General Correspondence | General Correspondence: Subject: Request for SPA |
| IND 63,736 - 121 | 119 | 16-Sep-05 | Safety Report | Safety Report: Report#{ ( Report#: S05-JPN-03246-01; ; Follow-up#: ); } |
| IND 63,736 - 122 | 120 | 19-Sep-05 | General Correspondence | General Correspondence: Subject: Delineation of Responsibilities - FMS031 and FMS034 |

# IND Submission Log

| Record ID | S/N | Date | Record Type(s) | Summary |
|---|---|---|---|---|
| IND 63,736 - 123 | 121 | 19-Sep-05 | Information Amendment | Information Amendment: Choose From:( Clinical ); Clinical{ ( Study Report Number: FMS-031; Protocol Number: FMS-031; Date of Clinical Study Report: 16-SEP-2005; Report Type: ); }; |
| IND 63,736 - 124 | 122 | 20-Sep-05 | Protocol Amendment | Protocol Amendment: RE:( Change in Protocol ); Change in Protocal{ Version Date: 15-SEP-2005; ( Protocol Number: MLN-PK-10 ); }; |
| IND 63,736 - 125 | 123 | 20-Sep-05 | Safety Report | Safety Report: Report#{ ( Report#: T05-USA-02137-01; ; Follow-up#: ); } |
| IND 63,736 - 126 | 124 | 28-Sep-05 | Safety Report | Safety Report: Report#{ ( Report#: T05-USA-03480-01; ; Follow-up#: ); } |
| IND 63,736 - 127 | 125 | 30-Sep-05 | Safety Report | Safety Report: Report#{ ( Report#: T05-USA-03480-01; ; Follow-up#: ); } |
| IND 63,736 - 128 | 126 | 3-Oct-05 | Safety Report | Safety Report: Report#{ ( Report#: T05-USA-02137-01, S05-JPN-02374-01; Follow-up, ; Follow-up#: 1, ); } |
| IND 63,736 - 129 | 127 | 6-Oct-05 | Safety Report | Safety Report: Report#{ ( Report#: T05-USA-03480-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 130 | 128 | 11-Oct-05 | General Correspondence | General Correspondence: Subject: General Correspondence - Telephone Discussion with Jane Dean 10-5-05 |
| IND 63,736 - 131 | 129 | 11-Oct-05 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-04 ); }; |
| IND 63,736 - 132 | 130 | 14-Oct-05 | Safety Report | Safety Report: Report#{ ( Report#: S05-FRA-03702-01; ; Follow-up#: ); } |
| IND 63,736 - 134 | 131 | 21-Oct-05 | Safety Report | Safety Report: Report#{ ( Report#: T04-o7742-01; Follow-up; Follow-up#: 4 ); } |
| IND 63,736 - 135 | 132 | 27-Oct-05 | Protocol Amendment | Protocol Amendment: RE:( Change in Protocol; New Investigator; New Protocol ); Change in Protocal{ Version Date: 07-OCT-2005; ( Protocol Number: MLN-PK-04 ); }; New Investigator{ ( Protocol Number: MLN-PK-04 ); }; New Protocol{ Version Date: 30-SEP-2005; ( Protocol Number: MLN-PK-04 ); }; |
| IND 63,736 - 136 | 133 | 7-Nov-05 | Information Amendment | Information Amendment: Choose From:( Pharmacology Toxicology ); Toxicology Report Number{ ( Toxicology Report Number: T025, T093, P154, P181, P167, P180 ); } |
| IND 63,736 - 137 | 134 | 17-Nov-05 | General Correspondence | General Correspondence: Subject: We are requesting a Type C meeting with the Divisionâ€™s Medical and Statistical Reviewers to obtain the Agencyâ€™s feedback regarding our Phase III program. |
| IND 63,736 - 138 | 135 | 22-Nov-05 | Response to FDA | Response to FDA: Choose From:( Pharmacology Toxicology ); |
| IND 63,736 - 139 | 136 | 2-Dec-05 | Safety Report | Safety Report: Report#{ ( Report#: T05-USA-05517-01; ; Follow-up#: ); } |
| IND 63,736 - 140 | 137 | 16-Dec-05 | Safety Report | Safety Report: Report#{ ( Report#: T05-USA-05517-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 141 | 138 | 21-Dec-05 | Safety Report | Safety Report: Report#{ ( Report#: S05-FRA-05686-02; ; Follow-up#: ); } |
| IND 63,736 - 142 | 139 | 5-Jan-06 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-04 ); }; |
| IND 63,736 - 143 | 140 | 6-Jan-06 | Safety Report | Safety Report: Report#{ ( Report#: T05-USA-03551-01, T05-USA-05517-01; , Follow-up; Follow-up#: , 2 ); } |

# IND Submission Log

| Record ID | S/N | Date | Record Type(s) | Summary |
|---|---|---|---|---|
| IND 63,736 - 144 | 141 | 10-Jan-06 | Protocol Amendment | Protocol Amendment: RE:( Change in Protocol ); Change in Protocal{ Version Date: 01-DEC-2005; ( Protocol Number: MLN-PK-10 ); }; |
| IND 63,736 - 145 | 142 | 16-Jan-06 | Protocol Amendment | Protocol Amendment: RE:( Change in Protocol; New Investigator; New Protocol ); Change in Protocal{ Version Date: 27-DEC-2005; ( Protocol Number: MLN-PK-07 ); }; New Investigator{ ( Protocol Number: MLN-PK-07 ); }; New Protocol{ Version Date: 08-DEC-2005; ( Protocol Number: MLN-PK-07 ); }; |
| IND 63,736 - 146 | 143 | 7-Feb-06 | Safety Report | Safety Report: Report#{ ( Report#: T05-USA-03551-01; ; Follow-up#: ); } |
| IND 63,736 - 147 | 144 | 8-Feb-06 | Safety Report | Safety Report: Report#{ ( Report#: T05-USA-03551-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 148 | 145 | 21-Feb-06 | Safety Report | Safety Report: Report#{ ( Report#: T06-USA-00037-01; ; Follow-up#: ); } |
| IND 63,736 - 149 | 146 | 24-Feb-06 | Safety Report | Safety Report: Report#{ ( Report#: T06-USA-00037-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 150 | 147 | 24-Feb-06 | Protocol Amendment | Protocol Amendment: RE:( Change in Protocol ); Change in Protocal{ Version Date: 26-JAN-2006; ( Protocol Number: MLN-MD-02 ); }; |
| IND 63,736 - 152 | 148 | 3-Mar-06 | Annual Report | Annual Report: From: 02-JAN-2005; To: 01-JAN-2006 |
| IND 63,736 - 153 | 149 | 6-Mar-06 | Protocol Amendment | Protocol Amendment: RE:( New Investigator; New Protocol ); New Investigator{ ( Protocol Number: MLN-PK-08 ); }; New Protocol{ Version Date: 22-FEB-2006; ( Protocol Number: MLN-PK-08 ); }; |
| IND 63,736 - 154 | 150 | 9-Mar-06 | Safety Report | Safety Report: Report#{ ( Report#: T06-USA-00618-01; ; Follow-up#: ); } |
| IND 63,736 - 155 | 151 | 17-Mar-06 | Protocol Amendment | Protocol Amendment: RE:( New Investigator; Revised 1572 ); New Investigator{ ( Protocol Number: FMS-031 ); }; Revised 1572{ ( Protocol Number: FMS-034, MLN MD-02, MLN-MD-04 ); } |
| IND 63,736 - 156 | 152 | 21-Mar-06 | General Correspondence | General Correspondence: Subject: We are requesting a Type C meeting with the Divisionâ€™s Medical and Statistical Reviewers to obtain the Agencyâ€™s feedback regarding our Phase III program. |
| IND 63,736 - 157 | 153 | 29-Mar-06 | Safety Report | Safety Report: Report#{ ( Report#: S06-FRA-01250-01, T06-USA-00618-01; , Follow-up; Follow-up#: , 1 ); } |
| IND 63,736 - 158 | 154 | 4-Apr-06 | Protocol Amendment | Protocol Amendment: RE:( New Protocol ); New Protocol{ Version Date: 02-MAR-2006; ( Protocol Number: MLN-MD-03 ); }; |
| IND 63,736 - 159 | 155 | 12-Apr-06 | Safety Report | Safety Report: Report#{ ( Report#: T06-USA-01238-01; ; Follow-up#: ); } |
| IND 63,736 - 160 | 156 | 19-Apr-06 | Safety Report | Safety Report: Report#{ ( Report#: T06-USA-01238-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 161 | 157 | 2-May-06 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-02, MLN-MD-04 ); }; |
| IND 63,736 - 162 | 158 | 5-May-06 | Safety Report | Safety Report: Report#{ ( Report#: S06-JPN-01763-01; ; Follow-up#: ); } |
| IND 63,736 - 163 | 159 | 15-May-06 | Safety Report | Safety Report: Report#{ ( Report#: S06-JPN-01797-01; ; Follow-up#: ); } |
| IND 63,736 - 164 | 160 | 31-May-06 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-02, MLN-MD-03, MLN-MD-04 ); }; |

# IND Submission Log

| Record ID | S/N | Date | Record Type(s) | Summary |
|---|---|---|---|---|
| IND 63,736 - 165 | 161 | 6-Jun-06 | Safety Report | Safety Report: Report#{ ( Report#: S06-FRA-02178-01, S06-FRA-02177-01; , ; Follow-up#: , ); } |
| IND 63,736 - 166 | 162 | 7-Jun-06 | Safety Report | Safety Report: Report#{ ( Report#: S06-FRA-02187-01; ; Follow-up#: ); } |
| IND 63,736 - 167 | 163 | 7-Jun-06 | General Correspondence | General Correspondence: Subject: Sponsor Meeting Minutes from June 2, 2006 Meeting |
| IND 63,736 - 168 | 164 | 12-Jun-06 | Safety Report | Safety Report: Report#{ ( Report#: S06-FRA-02177-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 169 | 165 | 14-Jun-06 | Safety Report | Safety Report: Report#{ ( Report#: S06-FRA-02358-01; ; Follow-up#: ); } |
| IND 63,736 - 170 | 166 | 22-Jun-06 | Safety Report | Safety Report: Report#{ ( Report#: S06-JPN-01797-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 171 | 167 | 27-Jun-06 | Safety Report | Safety Report: Report#{ ( Report#: T06-USA-02409-01; ; Follow-up#: ); } |
| IND 63,736 - 172 | 168 | 30-Jun-06 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-02, MLN-MD-03 ); }; |
| IND 63,736 - 173 | 169 | 19-Jul-06 | Safety Report | Safety Report: Report#{ ( Report#: T06-USA-02409-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 174 | 170 | 25-Jul-06 | Safety Report | Safety Report: Report#{ ( Report#: S06-JPN-02903-01; ; Follow-up#: ); } |
| IND 63,736 - 175 | 171 | 26-Jul-06 | Safety Report | Safety Report: Report#{ ( Report#: S06-FRA-02358-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 176 | 172 | 31-Jul-06 | Safety Report | Safety Report: Report#{ ( Report#: S06-FRA-02358-01; Follow-up; Follow-up#: 2 ); } |
| IND 63,736 - 177 | 173 | 31-Jul-06 | Information Amendment | Information Amendment: Choose From:( Clinical ); Clinical{ Investigator's Brochure Date: 22-DEC-2004; ( Study Report Number: FDA PHA; Protocol Number: FDA PHA; Date of Clinical Study Report: 19-JUL-2006; Report Type: Full ); }; |
| IND 63,736 - 178 | 174 | 4-Aug-06 | Safety Report | Safety Report: Report#{ ( Report#: S06-JPN-03099-01; ; Follow-up#: ); } |
| IND 63,736 - 179 | 175 | 10-Aug-06 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-02, MLN-MD-03 ); }; |
| IND 63,736 - 180 | 176 | 14-Aug-06 | General Correspondence | General Correspondence: Subject: General Correspondence - Request for a Waiver of In Vivo Bioequivalence Study between Milnacipran HC1 Immediate Release Capsules and Tablets |
| IND 63,736 - 181 | 177 | 15-Aug-06 | Information Amendment | Information Amendment: Choose From:( Clinical ); Clinical{ ( Study Report Number: FMS-034; Protocol Number: FMS-034; Date of Clinical Study Report: 15-AUG-2006; Report Type: ); }; |
| IND 63,736 - 182 | 178 | 16-Aug-06 | Safety Report | Safety Report: Report#{ ( Report#: S06-FRA-03309-01; ; Follow-up#: ); } |
| IND 63,736 - 183 | 179 | 22-Aug-06 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-03 ); }; |

# IND Submission Log

| Record ID | S/N | Date | Record Type(s) | Summary |
|---|---|---|---|---|
| IND 63,736 - 184 | 180 | 23-Aug-06 | Protocol Amendment, Informatio | Information Amendment: Choose From:( Clinical ); Clinical{ ( Study Report Number: MLN-MD-02; Protocol Number: MLN-MD-02; Date of Clinical Study Report: 23-AUG-2006; Report Type: ); }; Protocol Amendment: RE:( Change in Protocol ); Change in Protocal{ Version Date: 23-AUG-2006; ( Protocol Number: MLN-MD-02 ); }; |
| IND 63,736 - 185 | 181 | 29-Aug-06 | Safety Report | Safety Report: Report#{ ( Report#: S06-FRA-03392-01; ; Follow-up#: ); } |
| IND 63,736 - 186 | 182 | 15-Sep-06 | Information Amendment | Information Amendment: Choose From:( CMC ); |
| IND 63,736 - 187 | 183 | 19-Sep-06 | Protocol Amendment | Protocol Amendment: RE:( New Protocol ); New Protocol{ Version Date: 06-SEP-2006; ( Protocol Number: MLN-PK-14 ); }; |
| IND 63,736 - 188 | 184 | 21-Sep-06 | Protocol Amendment | Protocol Amendment: RE:( New Protocol ); New Protocol{ Version Date: 24-AUG-2006; ( Protocol Number: MLN-MD-06 ); }; |
| IND 63,736 - 189 | 185 | 21-Sep-06 | Safety Report | Safety Report: Report#{ ( Report#: S06-JPN-02903-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 190 | 186 | 28-Sep-06 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-03, MLN-MD-04 ); }; |
| IND 63,736 - 191 | 187 | 11-Oct-06 | Safety Report | Safety Report: Report#{ ( Report#: T06-USA-02409-01; Follow-up; Follow-up#: 2 ); } |
| IND 63,736 - 192 | 188 | 11-Oct-06 | Protocol Amendment | Protocol Amendment: RE:( Change in Protocol ); Change in Protocal{ Version Date: 06-OCT-2006; ( Protocol Number: MLN-MD-03 ); }; |
| IND 63,736 - 193 | 189 | 17-Oct-06 | Safety Report | Safety Report: Report#{ ( Report#: T06-GER-04254-01, T05-USA-02137-01, T04-USA-07351-01, T04-USA-07603-01, T04-USA-07742-01; , Follow-up, Follow-up, Follow-up, Follow-up; Follow-up#: , 2, 2, 3, 5 ); } |
| IND 63,736 - 194 | 190 | 20-Oct-06 | General Correspondence | General Correspondence: Subject: General Correspondence: Request for Type C Meeting - Statistical Analysis Plan (SAP) for Study MLN-MD-02 |
| IND 63,736 - 195 | 191 | 24-Oct-06 | Safety Report | Safety Report: Report#{ ( Report#: S05-JPN-02374-01, T06-USA-02409-01; Follow-up, Follow-up; Follow-up#: 1, 3 ); } |
| IND 63,736 - 196 | 192 | 26-Oct-06 | Safety Report | Safety Report: Report#{ ( Report#: S06-FRA-03942-01; ; Follow-up#: ); } |
| IND 63,736 - 197 | 193 | 31-Oct-06 | Safety Report | Safety Report: Report#{ ( Report#: S06-JPN-04542-01; ; Follow-up#: ); } |
| IND 63,736 - 198 | 194 | 1-Nov-06 | Safety Report | Safety Report: Report#{ ( Report#: S06-JPN-04543-01; ; Follow-up#: ); } |
| IND 63,736 - 199 | 195 | 1-Nov-06 | Protocol Amendment | Protocol Amendment: RE:( Change in Protocol; New Investigator ); Change in Protocal{ Version Date: 06-OCT-2006; ( Protocol Number: MLN-PK-02 ); }; New Investigator{ ( Protocol Number: MLN-PK-02 ); }; |
| IND 63,736 - 200 | 196 | 6-Nov-06 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-02, MLN-MD-04 ); }; |
| IND 63,736 - 201 | 197 | 7-Nov-06 | Safety Report | Safety Report: Report#{ ( Report#: T06-GER-04254-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 202 | 198 | 9-Nov-06 | Safety Report | Safety Report: Report#{ ( Report#: S06-JPN-04703-01, S06-JPN-04704-01, S06-JPN-04704-02, S06-JPN-04705-01; , , , ; Follow-up#: , , , ); } |

# IND Submission Log

| Record ID | S/N | Date | Record Type(s) | Summary |
|---|---|---|---|---|
| IND 63,736 - 203 | 199 | 14-Nov-06 | Safety Report | Safety Report: Report#{ ( Report#: S06-JPN-04542-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 204 | 200 | 1-Dec-06 | General Correspondence | General Correspondence: Subject: Request for Feedback -Statistical Analysis Plan (SAP) - Study MLN-MD-02 |
| IND 63,736 - 205 | 201 | 12-Dec-06 | Safety Report | Safety Report: Report#{ ( Report#: S06-FRA-05157-01; ; Follow-up#: ); } |
| IND 63,736 - 206 | 202 | 12-Dec-06 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-06 ); }; |
| IND 63,736 - 207 | 203 | 14-Dec-06 | Safety Report | Safety Report: Report#{ ( Report#: S06-FRA-05156-01; ; Follow-up#: ); } |
| IND 63,736 - 208 | 204 | 14-Dec-06 | Information Amendment | Information Amendment: Choose From:( Clinical ); Clinical{ Investigator's Brochure Date: 29-NOV-2006; ( Study Report Number: MLN-MD-06; Protocol Number: MLN-MD-06; Date of Clinical Study Report: 14-DEC-2006; Report Type: ); }; |
| IND 63,736 - 209 | 205 | 15-Dec-06 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-06 ); }; |
| IND 63,736 - 210 | 206 | 21-Dec-06 | Information Amendment | Information Amendment: Choose From:( CMC ); |
| IND 63,736 - 211 | 207 | 21-Dec-06 | Safety Report | Safety Report: Report#{ ( Report#: S05-JPN-02374-01; Follow-up; Follow-up#: 2 ); } |
| IND 63,736 - 212 | 208 | 21-Dec-06 | General Correspondence | General Correspondence: Subject: General Correspondence: Request for Pre-NDA (Type B) Meeting |
| IND 63,736 - 213 | 209 | 27-Dec-06 | Safety Report | Safety Report: Report#{ ( Report#: S06-JPN-04705-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 214 | 210 | 2-Jan-07 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-02, MLN-MD-04 ); }; |
| IND 63,736 - 215 | 211 | 2-Jan-07 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-03 ); }; |
| IND 63,736 - 216 | 212 | 4-Jan-07 | Protocol Amendment | Protocol Amendment: RE:( New Investigator; New Protocol ); New Investigator{ ( Protocol Number: MLN-PK-15 ); }; New Protocol{ Version Date: 30-NOV-2006; ( Protocol Number: MLN-PK-15 ); }; |
| IND 63,736 - 217 | 213 | 10-Jan-07 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-06 ); }; |
| IND 63,736 - 218 | 214 | 16-Jan-07 | Safety Report | Safety Report: Report#{ ( Report#: S06-FRA-03942-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 219 | 215 | 17-Jan-07 | Safety Report | Safety Report: Report#{ ( Report#: T07-USA-00152-01; ; Follow-up#: ); } |
| IND 63,736 - 221 | 216 | 18-Jan-07 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-06 ); }; |
| IND 63,736 - 222 | 217 | 22-Jan-07 | Safety Report | Safety Report: Report#{ ( Report#: S07-FRA-00255-01; ; Follow-up#: ); } |
| IND 63,736 - 223 | 218 | 23-Jan-07 | Safety Report | Safety Report: Report#{ ( Report#: T06-USA-00618-01, T07-USA-00152-01; Follow-up, Follow-up; Follow-up#: 2, 1 ); } |
| IND 63,736 - 224 | 219 | 1-Feb-07 | Safety Report | Safety Report: Report#{ ( Report#: S07-FRA-00419-01; ; Follow-up#: ); } |

# IND Submission Log

| Record ID | S/N | Date | Record Type(s) | Summary |
|---|---|---|---|---|
| IND 63,736 - 225 | 220 | 5-Feb-07 | Safety Report | Safety Report: Report#{ ( Report#: T07-USA-00152-01; Follow-up; Follow-up#: 2 ); } |
| IND 63,736 - 226 | 221 | 12-Feb-07 | General Correspondence | General Correspondence: Subject: General Correspondence: Briefing Book for Pre-NDA Meeting - March 16, 2007 |
| IND 63,736 - 227 | 222 | 23-Feb-07 | Safety Report | Safety Report: Report#{ ( Report#: S06-FRA-05157-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 228 | 223 | 26-Feb-07 | Response to FDA | Response to FDA: Choose From:( Clinical ); |
| IND 63,736 - 229 | 224 | 27-Feb-07 | Protocol Amendment | Protocol Amendment: RE:( Change in Protocol ); Change in Protocal{ Version Date: 02-OCT-2003; ( Protocol Number: FMS-031 ); }; |
| IND 63,736 - 230 | 225 | 5-Mar-07 | Annual Report | Annual Report: From: 02-JAN-2006; To: 01-JAN-2007 |
| IND 63,736 - 231 | 226 | 14-Mar-07 | Safety Report | Safety Report: Report#{ ( Report#: S07-JPN-01158-01; ; Follow-up#: ); } |
| IND 63,736 - 232 | 227 | 20-Mar-07 | Safety Report | Safety Report: Report#{ ( Report#: S06-JPN-04704-01, S06-JPN-04704-02, T07-FRA-01181-01; Follow-up, Follow-up, ; Follow-up#: 1, 1, ); } |
| IND 63,736 - 233 | 228 | 21-Mar-07 | Safety Report | Safety Report: Report#{ ( Report#: S04-JPN-06345-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 234 | 229 | 22-Mar-07 | Response to FDA | Response to FDA: Choose From:( Pharmacology Toxicology ); |
| IND 63,736 - 235 | 230 | 23-Mar-07 | Safety Report | Safety Report: Report#{ ( Report#: T07-USA-00152-01; Follow-up; Follow-up#: 3 ); } |
| IND 63,736 - 236 | 231 | 23-Mar-07 | General Correspondence | General Correspondence: Subject: Sponsor Pre-NDA Meeting Minutes from March 16, 2007 |
| IND 63,736 - 237 | 232 | 26-Mar-07 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-06 ); }; |
| IND 63,736 - 239 | 234 | 29-Mar-07 | Information Amendment | Information Amendment: Choose From:( Clinical ); Clinical{ ( Study Report Number: MLN-PK-10; Protocol Number: MLN-PK-10; Date of Clinical Study Report: 22-Mar-2007; Report Type: Full ); }; |
| IND 63,736 - 238 | 233 | 30-Mar-07 | Safety Report | Safety Report: Report#{ ( Report#: S07-JPN-01158-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 240 | 235 | 3-Apr-07 | Safety Report | Safety Report: Report#{ ( Report#: T07-USA-00152-01; Follow-up; Follow-up#: 4 ); } |
| IND 63,736 - 241 | 236 | 4-Apr-07 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-03 ); }; |
| IND 63,736 - 242 | 237 | 5-Apr-07 | Safety Report | Safety Report: Report#{ ( Report#: S06-JPN-04543-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 243 | 238 | 25-Apr-07 | Safety Report | Safety Report: Report#{ ( Report#: L07-FRA-01733-02, L07-FRA-01733-03, L07-FRA-01733-04, L07-FRA-01733-05, L07-FRA-01733-06, L07-FRA-01733-07, L07-FRA-01733-08, L07-FRA-01733-09, L07-FRA-01733-10, L07-FRA-01733-11, L07-FRA-01733-12, L07-FRA-01733-13, L07-FRA-01733-14; , , , , , , , , , , , , ; Follow-up#: , , , , , , , , , , , , ); } |

# IND Submission Log

| Record ID | S/N | Date | Record Type(s) | Summary |
|---|---|---|---|---|
| IND 63,736 - 244 | 239 | 27-Apr-07 | Safety Report | Safety Report: Report#{ ( Report#: L07-FRA-01733-07; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 245 | 240 | 1-May-07 | Safety Report | Safety Report: Report#{ ( Report#: T06-USA-00618-01; Follow-up; Follow-up#: 3 ); } |
| IND 63,736 - 246 | 241 | 1-May-07 | General Correspondence | General Correspondence: Subject: Additional Information Regarding Serial Nos. 238 and 239 |
| IND 63,736 - 247 | 242 | 2-May-07 | General Correspondence | General Correspondence: Subject: Response to Official Minutes from Pre-NDA Meeting |
| IND 63,736 - 248 | 243 | 4-May-07 | Safety Report | Safety Report: Report#{ ( Report#: T07-FRA-01181-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 249 | 244 | 8-May-07 | Safety Report | Safety Report: Report#{ ( Report#: L07-FRA-01733-07, S07-FRA-01872-01; Follow-up, ; Follow-up#: 2, ); } |
| IND 63,736 - 250 | 245 | 10-May-07 | Protocol Amendment, Informatio | Information Amendment: Choose From:( Clinical ); Clinical{ ( Study Report Number: MLN-MD-02; Protocol Number: MLN-MD-02; Date of Clinical Study Report: 08-MAY-2007; Report Type: Full ); }; Protocol Amendment: RE:( Change in Protocol ); Change in Protocal{ Version Date: 07-MAY-2007; ( Protocol Number: MLN-MD-02 ); }; |
| IND 63,736 - 251 | 246 | 15-May-07 | Safety Report | Safety Report: Report#{ ( Report#: T05-USA-01966-01, T05-USA-02053-01, T05-USA-03551-01, T05-USA-05517-01, T06-USA-00037-01; Follow-up, Follow-up, Follow-up, Follow-up, Follow-up; Follow-up#: 4, 2, 2, 3, 2 ); } |
| IND 63,736 - 252 | 247 | 16-May-07 | Information Amendment | Information Amendment: Choose From:( Clinical ); Clinical{ ( Study Report Number: MLN-MD-04; Protocol Number: MLN-MD-04; Date of Clinical Study Report: 19-SEP-2006; Report Type: Full ); }; |
| IND 63,736 - 253 | 248 | 17-May-07 | Safety Report | Safety Report: Report#{ ( Report#: S07-FRA-02068-01; ; Follow-up#: ); } |
| IND 63,736 - 254 | 249 | 18-May-07 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: FMS-021 ); }; |
| IND 63,736 - 255 | 250 | 22-May-07 | Safety Report | Safety Report: Report#{ ( Report#: T06-USA-00618-01, T06-USA-01238-01, T06-USA-02409-01; Follow-up, Follow-up, Follow-up; Follow-up#: 4, 2, 4 ); } |
| IND 63,736 - 256 | 251 | 24-May-07 | Safety Report | Safety Report: Report#{ ( Report#: S07-FRA-02064-01, S07-FRA-02069-01, S07-FRA-02150-01, S07-FRA-02151-01, SG7-FRA-02154-0 I, S07-FRA-02152-01; , , , , , ; Follow-up#: , , , , , ); } |
| IND 63,736 - 257 | 252 | 25-May-07 | Safety Report | Safety Report: Report#{ ( Report#: T07-SWE-02234-01, T07-USA-02112-01; , ; Follow-up#: , ); } |
| IND 63,736 - 258 | 253 | 31-May-07 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-06 ); }; |
| IND 63,736 - 259 | 254 | 31-May-07 | Safety Report | Safety Report: Report#{ ( Report#: S07-FRA-02296-01, S07-FRA-02343-01; , ; Follow-up#: , ); } |
| IND 63,736 - 260 | 255 | 7-Jun-07 | Safety Report | Safety Report: Report#{ ( Report#: T07-SWE-02234-01, T07-USA-02112-01; Follow-up, Follow-up; Follow-up#: 1, 1 ); } |

# IND Submission Log

| Record ID | S/N | Date | Record Type(s) | Summary |
|---|---|---|---|---|
| IND 63,736 - 261 | 256 | 14-Jun-07 | Safety Report | Safety Report: Report#{ ( Report#: T07-SWE-02234-01; Follow-up; Follow-up#: 2 ); } |
| IND 63,736 - 262 | 257 | 15-Jun-07 | Protocol Amendment | Protocol Amendment: RE:( Change in Protocol ); Change in Protocal{ Version Date: 30-JAN-2002; ( Protocol Number: FMS-021 ); }; |
| IND 63,736 - 263 | 258 | 19-Jun-07 | General Correspondence | General Correspondence: Subject: Forest and Cypress have completed two large Phase III studies in adult patients where safety and efficacy of milnacipran HCl in the treatment of fibromyalgia syndrome were demonstrated in adults Â°i8 years of age. |
| IND 63,736 - 264 | 259 | 22-Jun-07 | Safety Report | Safety Report: Report#{ ( Report#: T07-SWE-02234-01, T07-USA-02112-01; Follow-up, Follow-up; Follow-up#: 3, 2 ); } |
| IND 63,736 - 265 | 260 | 27-Jun-07 | General Correspondence | General Correspondence: Subject: As follow up to the Pre-NDA Meeting, we have an additional point of clarification with regard to the provision of safety narratives and CRFs in the NDA for SAEs, deaths, and dropouts due to adverse events (ADOs) from the Supporting Safety Data. |
| IND 63,736 - 266 | 261 | 2-Jul-07 | Safety Report | Safety Report: Report#{ ( Report#: T07-USA-02112-01; Follow-up; Follow-up#: 3 ); } |
| IND 63,736 - 267 | 262 | 2-Jul-07 | General Correspondence | General Correspondence: Subject: The purpose of this correspondence is to address the additional FDA comment |
| IND 63,736 - 268 | 263 | 6-Jul-07 | Safety Report | Safety Report: Report#{ ( Report#: S07-FRA-02880-01; ; Follow-up#: ); } |
| IND 63,736 - 269 | 264 | 12-Jul-07 | Safety Report | Safety Report: Report#{ ( Report#: S07-FRA-02880-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 270 | 265 | 16-Jul-07 | Safety Report | Safety Report: Report#{ ( Report#: S06-JPN-04542-01; Follow-up; Follow-up#: 2 ); } |
| IND 63,736 - 271 | 266 | 20-Jul-07 | Safety Report | Safety Report: Report#{ ( Report#: L07-FRA-01733-07; Follow-up; Follow-up#: 3 ); } |
| IND 63,736 - 272 | 267 | 31-Jul-07 | Safety Report | Safety Report: Report#{ ( Report#: L07-FRA-01733-07; Follow-up; Follow-up#: 4 ); } |
| IND 63,736 - 273 | 268 | 6-Aug-07 | General Correspondence | General Correspondence: Subject: Submission of Potential Brand Name for Review |
| IND 63,736 - 274 | 269 | 6-Aug-07 | Safety Report | Safety Report: Report#{ ( Report#: T07-USA-03210-01; ; Follow-up#: ); } |
| IND 63,736 - 275 | 270 | 10-Aug-07 | Safety Report | Safety Report: Report#{ ( Report#: T07-FRA-01181-01, S07-JPN-03388-01, S07-JPN-03387-01; Follow-up, , ; Follow-up#: 2, , ); } |
| IND 63,736 - 276 | 271 | 16-Aug-07 | Safety Report | Safety Report: Report#{ ( Report#: T07-USA-03210-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 277 | 272 | 22-Aug-07 | Safety Report | Safety Report: Report#{ ( Report#: S07-FRA-03533-01; ; Follow-up#: ); } |
| IND 63,736 - 278 | 273 | 23-Aug-07 | Protocol Amendment | Protocol Amendment: RE:( New Investigator; New Protocol ); New Investigator{ ( Protocol Number: FMS-OL1 ); }; New Protocol{ Version Date: 20-JAN-2002; ( Protocol Number: FMS-Ol1 ); }; |

## IND Submission Log

| Record ID | S/N | Date | Record Type(s) | Summary |
|---|---|---|---|---|
| IND 63,736 - 279 | 274 | 27-Aug-07 | Protocol Amendment | Protocol Amendment: RE:( New Protocol ); New Protocol{ Version Date: 10-AUG-2007; ( Protocol Number: MLN-MD-12 ); }; |
| IND 63,736 - 280 | 275 | 28-Aug-07 | Safety Report | Safety Report: Report#{ ( Report#: T07-SWE-03572-0 l, S04-JPN-06169-01; , Follow-up; Follow-up#: , 1 ); } |
| IND 63,736 - 281 | 276 | 29-Aug-07 | Safety Report | Safety Report: Report#{ ( Report#: S04-JPN-05862-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 282 | 277 | 30-Aug-07 | Safety Report | Safety Report: Report#{ ( Report#: S04-JPN-06169-01; Follow-up; Follow-up#: 2 ); } |
| IND 63,736 - 283 | 278 | 31-Aug-07 | Safety Report | Safety Report: Report#{ ( Report#: T07-FIN-03607-01, T07-SWE-03572-01; , Follow-up; Follow-up#: , 1 ); } |
| IND 63,736 - 284 | 279 | 7-Sep-07 | Safety Report | Safety Report: Report#{ ( Report#: S06-FRA-05157-01; Follow-up; Follow-up#: 2 ); } |
| IND 63,736 - 285 | 280 | 11-Sep-07 | Safety Report | Safety Report: Report#{ ( Report#: S07-JPN-03739-01; ; Follow-up#: ); } |
| IND 63,736 - 286 | 281 | 18-Sep-07 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-06 ); }; |
| IND 63,736 - 287 | 282 | 19-Sep-07 | Safety Report | Safety Report: Report#{ ( Report#: S04-JPN-05851-01, T07-SWE-02234-01; Follow-up, Follow-up; Follow-up#: 1, 4 ); } |
| IND 63,736 - 288 | 283 | 20-Sep-07 | Response to FDA | Response to FDA: Choose From:( Labeling ); |
| IND 63,736 - 289 | 284 | 21-Sep-07 | Safety Report | Safety Report: Report#{ ( Report#: T07-FIN-03607-01, T07-SWE-03572-01; Follow-up, Follow-up; Follow-up#: 1, 2 ); } |
| IND 63,736 - 290 | 285 | 26-Sep-07 | Protocol Amendment | Protocol Amendment: RE:( Change in Protocol ); Change in Protocal{ Version Date: 13-SEP-2007; ( Protocol Number: MLN-MD-12 ); }; |
| IND 63,736 - 291 | 286 | 27-Sep-07 | Information Amendment | Information Amendment: Choose From:( CMC ); |
| IND 63,736 - 292 | 287 | 2-Oct-07 | Safety Report | Safety Report: Report#{ ( Report#: S04-JPN-04820-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 293 | 288 | 4-Oct-07 | Protocol Amendment | Protocol Amendment: RE:( Change in Protocol ); Change in Protocal{ Version Date: 06-SEP-2007; ( Protocol Number: MLN-MD-03 ); }; |
| IND 63,736 - 294 | 289 | 4-Oct-07 | Protocol Amendment | Protocol Amendment: RE:( New Protocol ); New Protocol{ Version Date: 26-SEP-2007; ( Protocol Number: MLN-PK-13 ); }; |
| IND 63,736 - 295 | 290 | 4-Oct-07 | Safety Report | Safety Report: Report#{ ( Report#: L07-JPN-G5239-01; ; Follow-up#: ); } |
| IND 63,736 - 296 | 291 | 5-Oct-07 | Safety Report | Safety Report: Report#{ ( Report#: T07-USA-03210-01; Follow-up; Follow-up#: 2 ); } |
| IND 63,736 - 297 | 292 | 11-Oct-07 | Safety Report | Safety Report: Report#{ ( Report#: T07-SWE-03572-01; Follow-up; Follow-up#: 3 ); } |
| IND 63,736 - 298 | 293 | 16-Oct-07 | Safety Report | Safety Report: Report#{ ( Report#: T07-SWE-02234-01, T07-SWE-03572-01; Follow-up, Follow-up; Follow-up#: 5, 4 ); } |
| IND 63,736 - 299 | 294 | 25-Oct-07 | Safety Report | Safety Report: Report#{ ( Report#: S07-FRA-05632-01; ; Follow-up#: ); } |
| IND 63,736 - 300 | 295 | 30-Oct-07 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-12 ); }; |

# IND Submission Log

| Record ID | S/N | Date | Record Type(s) | Summary |
|---|---|---|---|---|
| IND 63,736 - 301 | 296 | 8-Nov-07 | Safety Report | Safety Report: Report#{ ( Report#: T07-USA-05666-01; ; Follow-up#: ); } |
| IND 63,736 - 302 | 297 | 12-Nov-07 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-12 ); }; |
| IND 63,736 - 303 | 298 | 13-Nov-07 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-06 ); }; |
| IND 63,736 - 304 | 299 | 14-Nov-07 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-02, MLN-MD-03 ); }; |
| IND 63,736 - 305 | 300 | 16-Nov-07 | Safety Report | Safety Report: Report#{ ( Report#: S04-JPN-04812-01, S04-JPN-048 14-01, S04-JPN-04998-01, S04-JPN-05553-01, S04-JPN-05614-01; Follow-up, Follow-up, Follow-up, Follow-up, Follow-up; Follow-up#: 1, 1, 1, 1, 1 ); } |
| IND 63,736 - 306 | 301 | 19-Nov-07 | Safety Report | Safety Report: Report#{ ( Report#: S07-FRA-05959-02, T07-USA-05666-01; , Follow-up; Follow-up#: , 1 ); } |
| IND 63,736 - 307 | 302 | 26-Nov-07 | Safety Report | Safety Report: Report#{ ( Report#: T07-FIN-03607-01; Follow-up; Follow-up#: 2 ); } |
| IND 63,736 - 308 | 303 | 28-Nov-07 | Safety Report | Safety Report: Report#{ ( Report#: S04-JPN-06162-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 309 | 304 | 28-Nov-07 | Information Amendment | Information Amendment: Choose From:( CMC ); |
| IND 63,736 - 310 | 305 | 29-Nov-07 | Protocol Amendment | Protocol Amendment: RE:( New Investigator; New Protocol ); New Investigator{ ( Protocol Number: MLN-PK-17 ); }; New Protocol{ Version Date: 02-NOV-2007; ( Protocol Number: MLN-PK-17 ); }; |
| IND 63,736 - 311 | 306 | 3-Dec-07 | Safety Report | Safety Report: Report#{ ( Report#: L07-JPN-06147-01; ; Follow-up#: ); } |
| IND 63,736 - 312 | 307 | 4-Dec-07 | Safety Report | Safety Report: Report#{ ( Report#: L07-JPN-05239-01, T07-SWE-03572-01; Follow-up, Follow-up; Follow-up#: 1, 5 ); } |
| IND 63,736 - 313 | 308 | 10-Dec-07 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-06 ); }; |
| IND 63,736 - 314 | 309 | 11-Dec-07 | Safety Report | Safety Report: Report#{ ( Report#: L07-JPN-06262-01; ; Follow-up#: ); } |
| IND 63,736 - 315 | 310 | 13-Dec-07 | Safety Report | Safety Report: Report#{ ( Report#: T07-SWE-03572-01; Follow-up; Follow-up#: 6 ); } |
| IND 63,736 - 316 | 311 | 18-Dec-07 | Safety Report | Safety Report: Report#{ ( Report#: S07-FRA-06261-01, S07-JPN-06308-01; , ; Follow-up#: , ); } |
| IND 63,736 - 317 | 312 | 20-Dec-07 | Safety Report | Safety Report: Report#{ ( Report#: L07-JPN-06262-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 318 | 313 | 21-Dec-07 | Safety Report | Safety Report: Report#{ ( Report#: S07-FRA-06295-01, T07-SWE-02234-01; , Follow-up; Follow-up#: , 6 ); } |
| IND 63,736 - 319 | 314 | 27-Dec-07 | Safety Report | Safety Report: Report#{ ( Report#: S07-FRA-06435-01; ; Follow-up#: ); } |
| IND 63,736 - 320 | 315 | 28-Dec-07 | Safety Report | Safety Report: Report#{ ( Report#: S07-CZE-06471-01, S07-JPN-06207-01; , ; Follow-up#: , ); } |
| IND 63,736 - 321 | 316 | 3-Jan-08 | Safety Report | Safety Report: Report#{ ( Report#: S07-FRA-06261-01, T07-SWE-02234-01; Follow-up, Follow-up; Follow-up#: 1, 7 ); } |

# IND Submission Log

| Record ID | S/N | Date | Record Type(s) | Summary |
|---|---|---|---|---|
| IND 63,736 - 322 | 317 | 4-Jan-08 | Safety Report | Safety Report: Report#{ ( Report#: S07-FRA-06295-0 ), T07-NOR-06482-01; Follow-up, ; Follow-up#: 1, ); } |
| IND 63,736 - 323 | 318 | 7-Jan-08 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-12 ); }; |
| IND 63,736 - 324 | 319 | 8-Jan-08 | Safety Report | Safety Report: Report#{ ( Report#: S07-FRA-06435-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 325 | 320 | 15-Jan-08 | Safety Report | Safety Report: Report#{ ( Report#: S08-JPN-00095-01; ; Follow-up#: ); } |
| IND 63,736 - 326 | 321 | 16-Jan-08 | Safety Report | Safety Report: Report#{ ( Report#: S07-FRA-06435-01; Follow-up; Follow-up#: 2 ); } |
| IND 63,736 - 327 | 322 | 22-Jan-08 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-12 ); }; |
| IND 63,736 - 328 | 323 | 25-Jan-08 | Safety Report | Safety Report: Report#{ ( Report#: L07-JPN-06147-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 329 | 324 | 6-Feb-08 | Safety Report | Safety Report: Report#{ ( Report#: L07-JPN-06147-01; Follow-up; Follow-up#: 2 ); } |
| IND 63,736 - 330 | 325 | 7-Feb-08 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-12 ); }; |
| IND 63,736 - 331 | 326 | 8-Feb-08 | Safety Report | Safety Report: Report#{ ( Report#: S07-JPN-06308-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 332 | 327 | 13-Feb-08 | Safety Report | Safety Report: Report#{ ( Report#: S06-3PN-04543-01, S07-JPN-03266-01, S07-JPN-03388-01, S07-JPN-03739-01, S08-JPN-00095-01; Follow-up, , Follow-up, Follow-up, Follow-up; Follow-up#: 2, , 1, 1, 1 ); } |
| IND 63,736 - 333 | 328 | 15-Feb-08 | Safety Report | Safety Report: Report#{ ( Report#: S06-JPN-03099-01, T08-USA-00405-01; Follow-up, ; Follow-up#: 1, ); } |
| IND 63,736 - 334 | 329 | 20-Feb-08 | Protocol Amendment | Protocol Amendment: RE:( Change in Protocol ); Change in Protocal{ Version Date: 18-JAN-2008; ( Protocol Number: MLN-MD-06 ); }; |
| IND 63,736 - 335 | 330 | 20-Feb-08 | Safety Report | Safety Report: Report#{ ( Report#: T08-POL-00622-01; ; Follow-up#: ); } |
| IND 63,736 - 336 | 331 | 21-Feb-08 | Safety Report | Safety Report: Report#{ ( Report#: S07-JPN-03388-01, S07-JPN-03739-01; Follow-up, Follow-up; Follow-up#: 2, 2 ); } |
| IND 63,736 - 337 | 332 | 25-Feb-08 | Safety Report | Safety Report: Report#{ ( Report#: T08-USA-00405-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 338 | 333 | 27-Feb-08 | Safety Report | Safety Report: Report#{ ( Report#: S07-CZE-06471-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 339 | 334 | 29-Feb-08 | Annual Report | Annual Report: From: 02-DEC-2006; To: 01-DEC-2007 |
| IND 63,736 - 341 | 335 | 29-Feb-08 | Safety Report | Safety Report: Report#{ ( Report#: S04-FRA-04580-01, S07-JPN-03266-01; Follow-up, Follow-up; Follow-up#: 1, 1 ); } |
| IND 63,736 - 342 | 336 | 6-Mar-08 | Safety Report | Safety Report: Report#{ ( Report#: T08-USA-00405-01; Follow-up; Follow-up#: 2 ); } |

# IND Submission Log

| Record ID | S/N | Date | Record Type(s) | Summary |
|---|---|---|---|---|
| IND 63,736 - 343 | 337 | 7-Mar-08 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-03, MLN-MD-06 ); }; |
| IND 63,736 - 344 | 338 | 7-Mar-08 | Safety Report | Safety Report: Report#{ ( Report#: T07-NOR-06482-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 345 | 339 | 18-Mar-08 | Safety Report | Safety Report: Report#{ ( Report#: T08-POL-00622-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 346 | 340 | 21-Mar-08 | Safety Report | Safety Report: Report#{ ( Report#: S07-JPN-03266-01; Follow-up; Follow-up#: 2 ); } |
| IND 63,736 - 347 | 341 | 26-Mar-08 | Safety Report | Safety Report: Report#{ ( Report#: S08-JPN-01174-01; ; Follow-up#: ); } |
| IND 63,736 - 349 | 343 | 27-Mar-08 | Safety Report | Safety Report: Report#{ ( Report#: S06-JPN-04543-01, S07-JPN-01158-01, S07-JPN-03388-01, S07-JPN-06308-01; Follow-up, Follow-up, Follow-up, Follow-up; Follow-up#: 3, 2, 3, 2 ); } |
| IND 63,736 - 348 | 342 | 28-Mar-08 | Safety Report | Safety Report: Report#{ ( Report#: SOS-JPN-01256-01; ; Follow-up#: ); } |
| IND 63,736 - 350 | 344 | 31-Mar-08 | Information Amendment | Information Amendment: Choose From:( Clinical ); Clinical{ Investigator's Brochure Date: 25-MAR-2008; ( Study Report Number: MLN-MD-12; Protocol Number: MLN-MD-12; Date of Clinical Study Report: 31-MAR-2008; Report Type: ); }; |
| IND 63,736 - 351 | 345 | 1-Apr-08 | Safety Report | Safety Report: Report#{ ( Report#: S07-FRA-05959-02; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 352 | 346 | 7-Apr-08 | Safety Report | Safety Report: Report#{ ( Report#: S07-JPN-01158-01; Follow-up; Follow-up#: 3 ); } |
| IND 63,736 - 353 | 347 | 9-Apr-08 | Safety Report | Safety Report: Report#{ ( Report#: T07-USA-03210-01; Follow-up; Follow-up#: 3 ); } |
| IND 63,736 - 354 | 348 | 11-Apr-08 | Information Amendment | Information Amendment: Choose From:( CMC ); |
| IND 63,736 - 355 | 349 | 14-Apr-08 | Protocol Amendment | Protocol Amendment: RE:( New Investigator; New Protocol ); New Investigator{ ( Protocol Number: MLN-PK-19 ); }; New Protocol{ Version Date: 18-MAR-2008; ( Protocol Number: MLN-PK-19 ); }; |
| IND 63,736 - 356 | 350 | 21-Apr-08 | Safety Report | Safety Report: Report#{ ( Report#: S08-JPN-01174-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 357 | 351 | 23-Apr-08 | Safety Report | Safety Report: Report#{ ( Report#: T08-U SA-01500-01; ; Follow-up#: ); } |
| IND 63,736 - 358 | 352 | 25-Apr-08 | Safety Report | Safety Report: Report#{ ( Report#: S08-JPN-01174-01; Follow-up; Follow-up#: 2 ); } |
| IND 63,736 - 359 | 353 | 30-Apr-08 | Safety Report | Safety Report: Report#{ ( Report#: S08-JPN-01256-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 360 | 354 | 2-May-08 | Safety Report | Safety Report: Report#{ ( Report#: S08-JPN-01596-01; ; Follow-up#: ); } |
| IND 63,736 - 361 | 355 | 5-May-08 | Safety Report | Safety Report: Report#{ ( Report#: S08-FRA-01615-01; ; Follow-up#: ); } |
| IND 63,736 - 362 | 356 | 6-May-08 | Safety Report | Safety Report: Report#{ ( Report#: TOS-USA-01500-0 I, S08-FRA-01647-01; Follow-up, ; Follow-up#: 1, ); } |

# IND Submission Log

| Record ID | S/N | Date | Record Type(s) | Summary |
|---|---|---|---|---|
| IND 63,736 - 363 | 357 | 8-May-08 | Protocol Amendment | Protocol Amendment: RE:( Change in Protocol ); Change in Protocal{ Version Date: 28-APR-2008; ( Protocol Number: MLN-PK-19 ); }; |
| IND 63,736 - 364 | 358 | 9-May-08 | General Correspondence | General Correspondence: Subject: Other â€“ Delineation of Responsibilities: Studies FMS031 and MLN-MD-02 |
| IND 63,736 - 365 | 359 | 16-May-08 | Safety Report | Safety Report: Report#{ ( Report#: SOS-JPN-01256-01; Follow-up; Follow-up#: 2 ); } |
| IND 63,736 - 366 | 360 | 5-Jun-08 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-06 ); }; |
| IND 63,736 - 367 | 361 | 5-Jun-08 | Safety Report | Safety Report: Report#{ ( Report#: S08-JPN-01596-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 368 | 362 | 12-Jun-08 | Safety Report | Safety Report: Report#{ ( Report#: S07-FRA-00419-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 369 | 363 | 18-Jun-08 | Safety Report | Safety Report: Report#{ ( Report#: S08-FRA-02096-01; ; Follow-up#: ); } |
| IND 63,736 - 370 | 364 | 23-Jun-08 | Safety Report | Safety Report: Report#{ ( Report#: S08-JPN-02046-01; ; Follow-up#: ); } |
| IND 63,736 - 371 | 365 | 27-Jun-08 | Safety Report | Safety Report: Report#{ ( Report#: S08-FRA-02096-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 372 | 366 | 30-Jun-08 | Safety Report | Safety Report: Report#{ ( Report#: S08-JPN-02046-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 373 | 367 | 8-Jul-08 | Safety Report | Safety Report: Report#{ ( Report#: L08-JPN-02284-01; ; Follow-up#: ); } |
| IND 63,736 - 374 | 368 | 10-Jul-08 | Safety Report | Safety Report: Report#{ ( Report#: L08-JPN-02284-01, S07-FRA-03533-01; Follow-up, Follow-up; Follow-up#: 1, 1 ); } |
| IND 63,736 - 375 | 369 | 11-Jul-08 | Safety Report | Safety Report: Report#{ ( Report#: L08-FRA-02345-01; ; Follow-up#: ); } |
| IND 63,736 - 376 | 370 | 16-Jul-08 | General Correspondence | General Correspondence: Subject: Reference is made to IND 63,736 â€“ Milnacipran HCl and the submission dated July 11, 2008 (Serial No. 369) of an Initial IND 15-Day IND Safety Report (Mfr. Report # L08-FRA-02345-01) for the fatal or life-threatening experience reported in the literature. |
| IND 63,736 - 377 | 371 | 18-Jul-08 | Safety Report | Safety Report: Report#{ ( Report#: T08-USA-01940-01; ; Follow-up#: ); } |
| IND 63,736 - 378 | 372 | 25-Jul-08 | Safety Report | Safety Report: Report#{ ( Report#: L08-JPN-02284-01; Follow-up; Follow-up#: 2 ); } |
| IND 63,736 - 379 | 373 | 31-Jul-08 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-06 ); }; |
| IND 63,736 - 380 | 374 | 1-Aug-08 | Safety Report | Safety Report: Report#{ ( Report#: S08-JPN-02046-01; Follow-up; Follow-up#: 2 ); } |
| IND 63,736 - 381 | 375 | 15-Aug-08 | Safety Report | Safety Report: Report#{ ( Report#: 1000000372, 1000000509, S08-JPN-02046-01; , , Follow-up; Follow-up#: , , 3 ); } |
| IND 63,736 - 382 | 376 | 21-Aug-08 | Safety Report | Safety Report: Report#{ ( Report#: 100000G509; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 383 | 377 | 22-Aug-08 | Safety Report | Safety Report: Report#{ ( Report#: 1000000372; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 384 | 378 | 27-Aug-08 | Safety Report | Safety Report: Report#{ ( Report#: 1000000594, T07-FIN-03607-01; , Follow-up; Follow-up#: , 3 ); } |

# IND Submission Log

| Record ID | S/N | Date | Record Type(s) | Summary |
|---|---|---|---|---|
| IND 63,736 - 386 | 380 | 8-Sep-08 | Safety Report | Safety Report: Report#{ ( Report#: 1000000595; ; Follow-up#: ); } |
| IND 63,736 - 387 | 381 | 10-Sep-08 | Safety Report | Safety Report: Report#{ ( Report#: 1000000833, S08-JPN-01596-01; , Follow-up; Follow-up#: , 2 ); } |
| IND 63,736 - 388 | 382 | 11-Sep-08 | Protocol Amendment | Protocol Amendment: RE:( Change in Protocol ); Change in Protocal{ Version Date: 03-SEP-2008; ( Protocol Number: MLN-MD-06 ); }; |
| IND 63,736 - 385 | 379 | 12-Sep-08 | Safety Report | Safety Report: Report#{ ( Report#: 1000000805, T08-USA-00405-01, 1000000938; , Follow-up, ; Follow-up#: , 3, ); } |
| IND 63,736 - 389 | 383 | 16-Sep-08 | Safety Report | Safety Report: Report#{ ( Report#: 1000000372, 1000000595; Follow-up, Follow-up; Follow-up#: 2, 1 ); } |
| IND 63,736 - 390 | 384 | 19-Sep-08 | Safety Report | Safety Report: Report#{ ( Report#: T08-USA-00405-01; Follow-up; Follow-up#: 4 ); } |
| IND 63,736 - 112 | 385 | 22-Sep-08 | Safety Report | Safety Report: Report#{ ( Report#: 1000001045 (0); ; Follow-up#: ); } |
| IND 63,736 - 133 | 386 | 23-Sep-08 | General Correspondence | General Correspondence: Subject: PROPOSED PEDIATRIC STUDY REQUEST (PPSR) |
| IND 63,736 - 151 | 387 | 26-Sep-08 | Safety Report | Safety Report: Report#{ ( Report#: 1000000509; Follow-up; Follow-up#: 2 ); } |
| IND 63,736 - 220 | 388 | 30-Sep-08 | Safety Report | Safety Report: Report#{ ( Report#: 1000000594, 1000001045; Follow-up, Follow-up; Follow-up#: 1, 1 ); } |
| IND 63,736 - 340 | 389 | 3-Oct-08 | Safety Report | Safety Report: Report#{ ( Report#: 1000000938; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 391 | 390 | 10-Oct-08 | Safety Report | Safety Report: Report#{ ( Report#: 1000001268, 1000001270; , ; Follow-up#: , ); } |
| IND 63,736 - 392 | 391 | 13-Oct-08 | Safety Report | Safety Report: Report#{ ( Report#: 1000001275; ; Follow-up#: ); } |
| IND 63,736 - 393 | 392 | 23-Oct-08 | Safety Report | Safety Report: Report#{ ( Report#: T08-USA-01940-01; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 394 | 393 | 28-Oct-08 | Information Amendment | Information Amendment: Choose From:( Clinical ); Clinical{ ( Study Report Number: MLN-MD-03; Protocol Number: 000000000000; Date of Clinical Study Report: 28-OCT-2008; Report Type: ); }; |
| IND 63,736 - 395 | 394 | 4-Nov-08 | Protocol Amendment | Protocol Amendment: RE:( New Protocol ); New Protocol{ Version Date: 17-JUL-2008; ( Protocol Number: MLN-MD-16 ); }; |
| IND 63,736 - 396 | 395 | 5-Nov-08 | Safety Report | Safety Report: Report#{ ( Report#: 1000001500; ; Follow-up#: ); } |
| IND 63,736 - 397 | 396 | 11-Nov-08 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-15 ); }; |
| IND 63,736 - 398 | 397 | 14-Nov-08 | Information Amendment | Information Amendment: Choose From:( CMC ); |
| IND 63,736 - 399 | 399 | 21-Nov-08 | Safety Report | Safety Report: Report#{ ( Report#: 1000001275; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 400 | 398 | 21-Nov-08 | Information Amendment | Information Amendment: Choose From:( Clinical ); Clinical{ Investigator's Brochure Date: 21-NOV-2008; ( Study Report Number: 00000, 00000; Protocol Number: MLN-MD-12, MLN-MD-12; Date of Clinical Study Report: 26-SEP-2008, 20-NOV-2008; Report Type: , ); }; |
| IND 63,736 - 401 | 400 | 1-Dec-08 | Safety Report | Safety Report: Report#{ ( Report#: T07-USA-03210-01; Follow-up; Follow-up#: 4 ); } |

# IND Submission Log

| Record ID | S/N | Date | Record Type(s) | Summary |
|---|---|---|---|---|
| IND 63,736 - 402 | 401 | 2-Dec-08 | Safety Report | Safety Report: Report#{ ( Report#: t07-usa-00152-01; Follow-up; Follow-up#: 5 ); } |
| IND 63,736 - 403 | 402 | 10-Dec-08 | Safety Report | Safety Report: Report#{ ( Report#: 1000003081; ; Follow-up#: ); } |
| IND 63,736 - 404 | 403 | 12-Dec-08 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-15, MLN-MD-16 ); }; |
| IND 63,736 - 405 | 404 | 5-Jan-09 | Safety Report | Safety Report: Report#{ ( Report#: 1000003349; ; Follow-up#: 0 ); } |
| IND 63,736 - 406 | 405 | 22-Jan-09 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-15 ); }; |
| IND 63,736 - 407 | 406 | 28-Jan-09 | Safety Report | Safety Report: Report#{ ( Report#: 1000003349; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 408 | 407 | 30-Jan-09 | Response to FDA | Response to FDA: Choose From:( General(all other) ); General{ Subject: Response to FDA Reequest for Information: Status of Study MLN-MD-06; } |
| IND 63,736 - 409 | 408 | 3-Feb-09 | Safety Report | Safety Report: Report#{ ( Report#: 1000003636; ; Follow-up#: ); } |
| IND 63,736 - 410 | 409 | 12-Feb-09 | Safety Report | Safety Report: Report#{ ( Report#: 1000003636; Follow-up; Follow-up#: 1 ); } |
| IND 63,736 - 411 | 410 | 17-Feb-09 | Safety Report | Safety Report: Report#{ ( Report#: 1000001275, T07-SWE-03572; Follow-up, ; Follow-up#: 2, ); } |
| IND 63,736 - 413 | 411 | 19-Feb-09 | Safety Report | Safety Report: Report#{ ( Report#: T08-USA-01500-01; Follow-up; Follow-up#: 2 ); } |
| IND 63,736 - 412 | 412 | 23-Feb-09 | Safety Report | Safety Report: Report#{ ( Report#: T08-USA-00405-01; Follow-up; Follow-up#: 5 ); } |
| IND 63,736 - 414 | 413 | 26-Feb-09 | Protocol Amendment | Protocol Amendment: RE:( New Investigator ); New Investigator{ ( Protocol Number: MLN-MD-15 ); }; |
| IND 63,736 - 415 | 415 | 27-Feb-09 | Safety Report | Safety Report: Report#{ ( Report#: 1000003636; Follow-up; Follow-up#: 2415 ); } |
| IND 63,736 - 416 | 414 | 27-Feb-09 | Annual Report | Annual Report: From: 02-DEC-2007; To: 01-DEC-2008 |

# EXHIBIT J

PTO/SB/26 (09-04)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE


**TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT**

Docket Number (Optional): 20269/1201776-US3

In re Application of: Jay D. Kranzler et al.

Application No.: 10/623,378

Filed: July 18, 2003

For: METHODS OF TREATING FIBROMYALGIA SYNDROME, CHRONIC FATIGUE SYNDROME AND PAIN

The owner*, Cypress Bioscience, Inc., of _____ percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of prior patent No. 6,602,911/6,635,675 as the term of said prior patent is defined in 35 U.S.C. 154 and 173, and as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 and 173 of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later:

expires for failure to pay a maintenance fee;
is held unenforceable;
is found invalid by a court of competent jurisdiction;
is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
has all claims canceled by a reexamination certificate;
is reissued; or
is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☐ For submissions on behalf of a business/organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the business/organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☒ The undersigned is an attorney or agent of record. Reg. No. 52,392

Signature — Date: June 14, 2005

Paul M. Zagar
Typed or printed name

(212) 527-7700
Telephone Number

☒ Terminal disclaimer fee under 37 CFR 1.20(d) is included.

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner). Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Express Mail Label No. Dated: _____

06/21/2005 TBESHAH1 00000058 10623378
01 FC:2814 65.00 OP

06/21/2005 TBESHAH1 00000023 10623378
01 FC:1814 130.00 OP

(W:\20269\1201776us3\00454087.DOC)

Void date: 06/21/2005 TBESHAH1
01 FC:1814 130.00 OP

PTO/SB/25(09-04)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE



| TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION | Docket Number (Optional) 20269/1201776-US3 |
|---|---|

In re Application of: Jay D. Kranzler et al.

Application No.: 10/623,378

Filed: July 18, 2003

For: METHODS OF TREATING FIBROMYALGIA SYNDROME, CHRONIC FATIGUE SYNDROME AND PAIN

The owner*, Cypress Bioscience, Inc., of _____ percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number 10/623,431, filed on July 18, 2003, as such term is defined in 35 U.S.C. 154 and 173, and as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 and 173 of any patent granted on said reference application, "as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application," in the event that: any such patent granted on the pending reference application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

Check either box 1 or 2 below, if appropriate.

1. ☐ For submissions on behalf of a business/organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the business/organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☒ The undersigned is an attorney or agent of record. Reg. No. 52,392

Signature — June 16, 2005 Date

Paul M. Zagar
Typed or printed name

(212) 527-7700
Telephone Number

☒ Terminal disclaimer fee under 37 CFR 1.20(d) is included.

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner). Form PTO/SB/96 may be used for making this statement. See MPEP § 324.

06/21/2005 TBESHAH1 00000058 10623378
02 FC:2814 65.00 OP

Express Mail Label No. Dated: _____

# EXHIBIT K

UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION

PATENT NO. : 6,992,110 B2
DATED : January 31, 2006
INVENTOR(S) : Jay D. Kranzler et al.

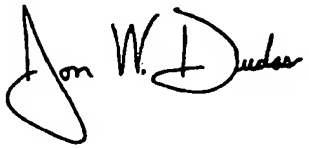


It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,
Item [*] Notice, insert -- This patent is subject to a Terminal Disclaimer --.

Signed and Sealed this

Ninth Day of May, 2006



JON W. DUDAS
*Director of the United States Patent and Trademark Office*